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This study evaluated the toxicity of WR238605 in dogs following thirteen weeks of daily oral (gavage) administration. A thirteen week recovery period was included for all groups. Dose levels studied were 0 (vehicle control), 0.1, 2.0 and 6.0 mg base/kg/day. The primary toxic effects of WR238605 were seen in the lungs and RBCs. Drug treatment was associated with hemolytic anemia which was supported by reticulocytosis, bone marrow hypercellularity, decrease in bone marrow M/E ratio, splenomegaly, extramedullary hematopoiesis, and hemosiderosis in the liver and spleen. Mild hepatotoxicity as evidenced by hepatocyte necrosis (high dose males) was supported by altered clinical chemistry values. Possibly, secondary to the hematologic alterations, congestion of retinal vessels was seen in one high dose female, which was no longer evident by the end of the recovery period. Generalized or secondary toxic effects related to the stress produced by the anemic and/or methemoglobinemic state included decreases in weight gain; neutrophilic and monocytic leukocytosis; and depletion of thymic lymphocytes. Methemoglobinemia was manifested by clinical signs of cyanosis (blue gums, tongue, and sclera). Lung lesions induced by WR238605 included alveolar proteinosis and subacute inflammation. Also, chronic inflammation of the alveolar and bronchiolar epithelium developed in the recovery period. This was deemed to be part of the process of resolution of alveolar proteinosis and as such a secondary lesion to a direct treatment-related effect. All of the above described toxic effects were generally seen at the high and mid dose levels. Hemosiderosis and subacute inflammation of the liver (minimal severity), secondary to hemolytic anemia, and bone marrow hypercellularity (minimal severity) were also seen in low dose animals. However, these findings in low dose animals were not supported by alterations in clinical pathology parameters. WR238605 toxicity was essentially reversible, except for the lung lesions (subacute inflammation) and the microscopic changes secondary to the observed hemolytic anemia (hepatic hemosiderosis). Based upon the these findings, the no observed effect level (NOEL) in this study was equivocal, but was considered to be near the low dose level of 0.1 mg base/kg/day.

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Title Page

Volume 1 of 3

Revised Draft Report for Task Order No. UIC-5A

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

Sponsor: US Army Medical Materiel Development Activity

Test Article: WR238605

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

June 11, 1993

Performing Laboratory

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DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-5A
UIC/TRL Study No.: 097

STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 097 entitled "Thirteen Week Oral Toxicity Study of WR 238605 with a Thirteen Week Recovery Period in Dogs" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

_____ _____

Barry S. Levine, D.Sc., D.A.B.T. Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

STUDY NUMBER: 097

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 9/1/92

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 9/1/92, TO STUDY DIR 9/1/92, TO MGMT 9/1/92
PHASES: PROTOCOL REVIEW
INSPECT ON 11/19/92, TO STUDY DIR 11/19/92, TO MGMT 11/19/92
PHASES: QUARANTINE AND ROOM ENVIRONMENT
INSPECT ON 1/5/93, TO STUDY DIR 1/6/93, TO MGMT 1/6/93
PHASES: BLOOD COLLECTION AND CLINICAL PATHOLOGY
INSPECT ON 3/9/93, TO STUDY DIR 3/10/93, TO MGMT 3/10/93
PHASES: ELECTROCARDIOGRAPHY
INSPECT ON 9/1/93, TO STUDY DIR 9/2/93, TO MGMT 9/8/93
PHASES: RAW DATA FROM ANALYTICAL LABORATORY
INSPECT ON 9/2/93, TO STUDY DIR 9/2/93, TO MGMT 9/8/93
PHASES: DRAFT REPORT FROM ANALYTICAL LABORATORY
INSPECT ON 9/10/93, TO STUDY DIR 9/10/93, TO MGMT 9/23/93
PHASES: CARDIOLOGY DRAFT REPORT
INSPECT ON 9/17/93, TO STUDY DIR 9/17/93, TO MGMT 9/17/93
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INSPECT ON 9/13-17/93, TO STUDY DIR 9/17/93, TO MGMT 9/27/93
PHASES: RAW DATA
INSPECT ON 9/30/93, TO STUDY DIR 9/30/93, TO MGMT 10/1/93
PHASES: DRAFT FINAL REPORT
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Ronald Schaenbeck 5/5/94

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Signature Page

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

TRL Chemical No.: 0720614

Sponsor: US Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5014

Sponsor
Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 W. Taylor St.
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_____ _____
Barry S. Levine, D.Sc., D.A.B.T. Date
Study Director

Study Initiation: September 1, 1992
Dosing Initiation: December 10, 1992
In-Life Completion: June 11, 1993

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1. SUMMARY

This study evaluated the toxicity of WR238605 in dogs following thirteen weeks of daily oral (gavage) administration. A thirteen week recovery period was included for all groups. Dose levels studied were 0 (vehicle control), 0.1, 2.0 and 6.0 mg base/kg/day. The results are summarized in Table 1. The primary toxic effects of WR238605 were seen in the lungs and RBCs. Drug treatment was associated with hemolytic anemia which was supported by reticulocytosis, bone marrow hypercellularity, decrease in bone marrow M/E ratio, splenomegaly, extramedullary hematopoiesis, and hemosiderosis in the liver and spleen. Mild hepatotoxicity as evidenced by hepatocyte necrosis (high dose males) was supported by altered clinical chemistry values. Possibly, secondary to the hematologic alterations, congestion of retinal vessels was seen in one high dose female, which was no longer evident by the end of the recovery period. Generalized or secondary toxic effects related to the stress produced by the anemic and/or methemoglobinemic state included decreases in weight gain; neutrophilic and monocytic leukocytosis; and depletion of thymic lymphocytes. Methemoglobinemia was manifested by clinical signs of cyanosis (blue gums, tongue, and sclera). Lung lesions induced by WR238605 included alveolar proteinosis and subacute inflammation. Also, chronic inflammation of the alveolar and bronchiolar epithelium developed in the recovery period. This was deemed to be part of the process of resolution of alveolar proteinosis and as such a secondary lesion to a direct treatment-related effect. All of the above described toxic effects were generally seen at the high and mid dose levels. Hemosiderosis and subacute inflammation of the liver (minimal severity), secondary to hemolytic anemia, and bone marrow hypercellularity (minimal severity) were also seen in low dose animals. However, these findings in low dose animals were not supported by alterations in clinical pathology parameters. WR238605 toxicity was essentially reversible, except for the lung lesions (subacute inflammation) and the microscopic changes secondary to the observed hemolytic anemia (hepatic hemosiderosis). Based upon the these findings, the no observed effect level (NOEL) in this study was equivocal, but was considered to be near the low dose level of 0.1 mg base/kg/day.

since similar effects was found in the control animals

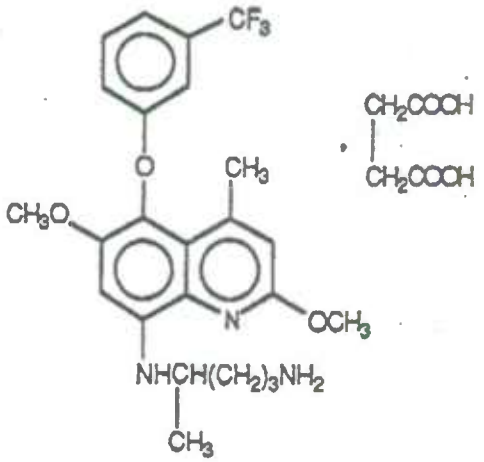
2. INTRODUCTION

This study was conducted to determine the specific target organ toxicity, dose-response relationships and a potential no-adverse effect level of WR238605 in dogs following thirteen weeks of daily oral (gavage) administration. A thirteen week recovery period was included for all groups to assess the reversibility of toxic effects. The study was conducted in accordance with the specifications of the Sponsor, as indicated in Task Order UIC-5A. The FDA requires the use of two animal species, one which is a non-rodent, in preclinical toxicology studies. The dog is a standard and accepted non-rodent species for regulatory toxicology studies, and was specified by the Sponsor. Oral administration is the intended clinical route and was also specified by the Sponsor. All methods and procedures were conducted in accordance with the Quality Assurance Programs of the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Inc. designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on December 10, 1992 and the in-life portion was terminated on June 11, 1993.

3. MATERIALS AND METHODS

3.1 Test Article

WR238605 succinate (Bottle Lot No. BM 12562), a fine, pale yellow powder, was received on October 5, 1992 from Herner & Co. The chemical name of the test article is 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethyl-phenoxy)quinoline succinate and the mole fraction of the base is 0.8. It was stored at 0 - 4°C, ambient humidity and protected from light in an amber bottle. The chemical structure is shown below.



WR238605 succinate

The test article was initially identified by GC-MS and the purity was determined to be greater than 99.9 %. The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was also greater than 99.9%. Thus, the test article was stable under storage conditions.

3.2 Animals

Thirty seven male and thirty seven female Beagle dogs were obtained from Marshall Farms, North Rose, NY on November 17 and 18, 1992. The animals were approximately 6 - 7 months old (dates of birth between 4/16/91 and 5/15/91) upon arrival at the UIC AAALAC-accredited animal facility. Each animal was given a facility-unique animal number upon arrival. This number immediately appeared as a tag on a chain collar, and was additionally tattooed in the inner aspect of the ear on the same day. Animals were singly housed in runs, except as subsequently noted, in a temperature (72 + 6°F) and humidity (50 $\pm$ 20%) controlled room with a 12 hour light/12 hour dark cycle. Eight dogs were housed two/run (within sex) during the quarantine/pretest period, but were singly housed prior to initiation of the dosing phase. The run size, typically at least 15 square feet, was adequate to house dogs at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All runs were cleaned and fresh bedding was replaced daily. The runs were sanitized once every two weeks.

Purina Certified Canine Diet No. 5007 (Ralston Purina Company, St. Louis, MO), approximately 400 g on a daily basis (exactly 400 g on days when food consumption was measured), and tap water *ad libitum* from an automatic watering system in which the room distribution lines were flushed daily were provided from arrival until termination. The water was untreated with additional chlorine or HCl. The food was removed for an overnight fast (≈ 16 - 20 hours) prior to blood collection for clinical pathology and/or scheduled sacrifice. There were no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

The animals were quarantined for three weeks. During that time, the animals were observed daily for signs of illness and all unusual observations were reported to the Study Director or Clinical Veterinarian. Body weights and preliminary physical examinations were done upon arrival at the animal facility. Each dog was lightly sprayed with Para Pyrethrin Mist upon arrival for fleas, lice, and ticks. All dogs were previously vaccinated by the animal supplier against canine distemper, infectious canine hepatitis, oral papilloma, leptospirosis, parainfluenza, parvo and rabies. Blood samples were collected within three days of arrival for quarantine clinical chemistry and hematology tests, and fecal samples were collected for internal parasites examinations. Animals were examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test. Quarantine release was documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

3.3 Experimental Design

Near the end of the quarantine/pretest period, 32 animals of each sex were selected for study on the basis of quarantine data including body weight, food consumption, clinical pathology, electrocardiograms, and ophthalmology examinations. These animals were randomized within sex into the groups shown in the following table using a restricted randomized procedure stratified by body weight. No litter mates were included in the same dose group, except for a control male and female. Following allocation to treatment groups, the animals were randomly assigned to one of six animal rooms used for this study.

Treatment Group	Dose Level (mg base/kg/day)	Number of Males	Number of Females
1	0	4 + 4*	4 + 4*
2	0.1	4 + 4*	4 + 4*
3	2.0	4 + 4*	4 + 4*
4	6.0	4 + 4*	4 + 4*

*Recovery Animals

Dose levels were supplied by the Sponsor and refer to the base.

Four animals/dose/sex were necropsied in Week 14 after 91 or 92 days of dosing. All remaining animals were held for a thirteen week recovery period, at which time they were necropsied. The number of animals/sex/group was necessary for adequate statistical analysis.

Following treatment group allocation, the animal's number appeared on a card visible on the front of each run. The run card additionally contained the study number, test article identification, treatment group number, sex and dose level. Run cards were color-coded as a function of treatment group.

Dosing formulations were prepared every 2 weeks by suspending an appropriate quantity of the test article in vehicle (aqueous 1% methylcellulose/0.4% Tween 80). Stability was based on data from a previously conducted dog toxicity study by gastric intubation (UIC/TRL Study No. 047). WR238605 dosage formulations were also shown to be homogeneous in that study. Samples of all dosage formulations used in Weeks 1 & 2, 7 & 8 and 13 were analyzed for test article concentration prior to their use. The results of these analyses are included in Table 2 and in Appendix 1.

The test article were suspended in the vehicle to result in concentrations necessary to administer the dosage formulations at a volume of 1 ml/kg. The specific volume (ml) administered was calculated on the basis of each animal's most recent body weight. The quantity of the test article was calculated as mg base/kg/day. The test article dosage formulation was administered by gastric intubation once daily for 91 or 92 days beginning on December 10, 1992 (Day 0). Following administration of the appropriate volume of the dosing formulations or vehicle, 20 ml of distilled water was administered to flush down any test article residuum. The animals were dosed up to and including the day prior to scheduled necropsy except for the recovery animals, which were dosed for 91 days. Control animals received the vehicle (aqueous 1% methylcellulose/0.4% Tween 80). The dogs weighed 9.6 - 11.3 kg (males) and 7.5 - 10.6 kg (females) on Day 0, and were approximately 7 - 8 months old at initiation of treatment.

Non-fasted body weights were recorded on Days -8 and 0, and weekly thereafter. Fasted weights were collected at scheduled termination. Clinical signs were recorded once daily, approximately 1 - 2 hours after dosing. The general behavior, posture, locomotion, breathing pattern and coat were observed for all animals. The animals were also observed immediately prior to dosing and in the afternoon for moribundity/mortality. During the recovery period, clinical signs were recorded once daily in the morning and a moribundity/mortality check was conducted in the afternoon. Physical examinations (clinical observations) which included examination of eyes and all orifices were conducted in Week -1, on Day 0 prior to dosing, and once weekly thereafter. Food consumption was measured for all animals over an approximate 24 hour period once weekly commencing with Week -2. All dogs were examined by indirect ophthalmoscopy prior to study initiation (Week -3) and during Week 13, and in Week 26 for the recovery animals. The eyes were dilated with 1% atropine sulfate

prior to the examination.

Hematology and clinical chemistry parameters were measured following an overnight fast in Weeks -3, -1, 2, 4, 8, and 13. Hematology and clinical chemistry tests were also performed for the recovery animals in Weeks 18 and 26. The overnight fasted animals were unanesthetized and sufficient blood was collected from the cephalic vein to measure the following parameters. The samples were processed in the same random order as collected. Water was available *ad libitum* during all fasting periods. Clinical pathology methodology is contained in Appendix 2.

Hematology

Activated partial thromboplastin time (APTT)	Mean corpuscular hemoglobin (MCH)
[a]Erythrocyte count and morphology	Mean corpuscular hemoglobin concentration (MCHC)
Heinz bodies	Mean corpuscular volume (MCV)
Hematocrit	[b]Methemoglobin
Hemoglobin	Platelet count
Leukocyte count, total and differential	Prothrombin time
	Reticulocyte count

[a]Includes nucleated RBCs.

[b]Measured with a Co-oximeter (Instrumentation Laboratory). The assay was performed within one hour of sample collection. The specimens were kept on wet ice prior to analysis.

Clinical Chemistry

Alanine aminotransferase (ALT/SGPT)	Gamma glutamyl transferase (GGT)
Albumin	Globulin (calculated)
Albumin/globulin ratio (calculated)	Glucose
Alkaline phosphatase	Haptoglobin
Aspartate aminotransferase (AST/SGOT)	Lactate dehydrogenase (LDH)
Calcium	Inorganic phosphorus
	Potassium
	Sodium

Clinical Chemistry (contd.)

Chloride	Total bilirubin
Cholesterol	Total protein
Creatinine	Triglycerides
Creatine kinase (CK)	Urea nitrogen (BUN)

Urine specimens were collected in Weeks -1, 2, 4, 8 and 13, and during the recovery period in Weeks 18 and 26. The following parameters were measured.

Urinalysis

Qualitative

Bilirubin	Nitrite
Glucose	pH
Ketones	Protein
Occult Blood	Urobilinogen
Leukocytes	

Color
Specific Gravity
Microscopic examination of spun sediment

Blood samples were also collected to provide approximately 1 ml of plasma for the measurement of drug levels in Weeks -1, 4, 8, 13, 18, and 26. The plasma samples were sent to Dr. Emil Lin as specified by the Sponsor. The results of the plasma drug level analysis are not included in this study report.

ECG tracings were collected from all dogs during the pretest period and in Week 13, and in Week 26 for the recovery animals. The following leads were measured: I, aV_F and V_3. Heart rate, PR and QT intervals were measured from Lead I. All recordings had a sensitivity of 1 mV/cm and a recording rate of 50 mm/sec. The recordings were made with the animal in the standard position of right lateral recumbency. In order to obtain all of the ECG's within a few days at each time point, the recordings were collected throughout the day during the baseline and recovery periods, but were performed in Week 13 in the afternoon, at least 2 hours after dosing.

Four animals/dose/sex were killed and necropsied in random order over a two consecutive day period (Days 91 and 92). The remaining recovery animals were killed and necropsied in random order at the onset of Week 27, after a thirteen week recovery period. This was accomplished by sodium pentobarbital anesthesia and exsanguination. An extensive necropsy was performed under the direction and supervision of the pathologist. Terminal body weights were collected prior to routine sacrifice.

The necropsy procedure was a thorough and systematic examination and dissection of the animal viscera and carcass to include the external surface, all orifices, the cranial cavity, external surface of the brain, cross section of the spinal cord, the nasal cavity and nasal turbinates, thoracic, abdominal and pelvic cavities and their viscera, and cervical tissues and organs. The following tissues and organs were collected and fixed in 10% neutral buffered formalin (NBF).

*Adrenal glands	Muscle, skeletal
Aorta (thoracic)	*Ovaries
*Brain	Pancreas
(fore-, mid-, and hind-)	Pituitary
Cecum	Prostate
Colon	Rib with marrow
Diaphragm	Rib with costochondral junction
Duodenum	Salivary gland (mandibular)
Esophagus	Sciatic Nerve
Eyes and optic nerve	Skin
Gallbladder	Spinal cord (thoracic)
Gross lesions	*Spleen
*Heart	Stomach
Ileum	*Testes with epididymides
Jejunum	Thymus
*Kidneys	*Thyroid gland with parathyroids
*Liver (with gallbladder	Tongue
drained)	Tonsil
Lungs/Bronchi	Trachea
Lymph node (submandibular	Ureter
and mesenteric)	Urinary bladder
Mammary gland	*Uterus

*Weighed at scheduled necropsy. Paired organs were weighed as a unit.

The above tissues from all dogs sacrificed at scheduled necropsy in Week 14 were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically. Those tissues/organs for which treatment-related lesions were observed were examined microscopically for all recovery animals.

Myeloid:erythroid (M:E) ratios were determined from a rib bone marrow smear for all animals at the Week 14 necropsy. Because treatment-related changes were seen at the end of the dosing period, M:E ratios were also determined from the recovery animals.

3.4 Statistical Analyses

For each sex, Analysis of Variance tests were conducted on body weight, weekly body weight gain, total body weight gains, ECG measurements, hematology, clinical chemistry and organ weight data. Organ weight analyses included absolute weights, and weights relative to both body and brain weights. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons with the concurrent control group . Food consumption data were analyzed by the Kruskal-Wallis test. If a significant effect was obtained ($p \leq 0.05$), the Mann-Whitney U test was used for pair-wise comparisons with the concurrent control group. All statistical analyses procedures compared treated to control animals at each time point. Data were not corrected for baseline values, except that body weight analysis included absolute values, weekly changes and total weight changes.

4. RESULTS

4.1 Dosage Formulation Analyses

Dosage formulation analysis results are shown in Table 2. The Analytical Chemistry Report is contained in Appendix 1. Only tested formulations which were within 10% of their target concentration were used. Although two of nine dosage formulations were initially not within 10% of their target concentration and were re-formulated for re-analysis, one of the dosage formulations was initially within 15%. Small variances therefore occurred in target concentrations, but were not considered to have an impact on the study. Since animals may gain or lose weight during the course of a week during which a single formulation is used, the exact dose (mg/kg/day) will vary as a function of time. It is typically assumed, however, that over the course of an entire study, small variances may occur in both directions. As such, any such changes probably are negligible over time, and the average dose received approximates the target dose.

4.2 Mortality/Clinical Signs

The summaries of clinical signs are presented in Table 3. Individual observations and daily incidence of clinical signs are contained in Appendix 3.

None of the dogs died in this study. Treatment-related clinical signs included blue tongue, blue gums and blue sclera in dogs at the mid and high doses except for one mid dose female. The severity of these signs were rated as follows: Slight (barely perceptible, slight blue tinged color; severity no. 1); Moderate (easily seen, blue color; severity no. 2); and Severe (marked, deep blue-purple color; severity no. 3). The onset of this cyanotic state was approximately 1 - 2 weeks after treatment initiation, and its severity progressed with time. The cyanotic state in mid and high dose animals was limited to moderate, easily seen blue gums, tongue, and sclera, except for one high dose

female (#7546) which demonstrated severe cyanosis as a marked, deep blue-purple tongue. The moderately severe (easily seen, blue color) clinical signs of cyanosis were observed at a greater frequency in high dose animals than in mid dose animals. In low dose animals, blue tongue (slight) was seen in one male and in four females, and blue sclera (slight) was observed in two males and in six females. Blue gums (slight) were also seen once in a low dose female. The biologic significance of these apparent signs of cyanosis seen in the low dose animals is uncertain.

In Week 11, two high dose males demonstrated signs of mild dehydration on three occasions. No other treatment-related clinical signs of toxicity were seen.

After cessation of treatment, the severity and incidence of these signs gradually decreased. In males, moderate blue tongue, gums and/or sclera were no longer observed after Day 92, however slight cyanotic features were observed up to Day 130. In females, the cyanotic state persisted for a longer duration. Moderate cyanosis, described as an easily seen blue tongue was seen until Day 114 and slight, barely perceptible blue tongue, sclera, and/or gums were seen until Week 7 of the recovery period. Thereafter, the occasional observation of a slight, barely perceptible blue tongue or sclera was not considered to be biologically significant. By the end of the recovery period, all clinical signs disappeared.

4.3 Body Weight

The summary of body weights are presented in Tables 4.1 - 4.4. The summary of weight gains are presented in Tables 5.1 - 5.4. Summaries of male and female body weights are also graphically depicted in Figures 1 and 2. Individual body weights and weight gains are contained in Appendix 4.

During the treatment period, decreased body weight gain and/or body weight loss was seen in mid and high dose animals (Tables 5.1 and 5.2). Although their rates of body weight gain were similar to control animals during the recovery period, their mean body weights remained somewhat lower than corresponding control animals, except possibly for mid dose males (Table 5.3 and 5.3). Body weights were unaffected in low dose animals.

4.4 Food Consumption

The summary of daily food consumption are in Tables 6.1 - 6.4. Individual food consumption data are shown in Appendix 5. Food consumption was not significantly affected in either sex by WR238605 treatment.

4.5 Clinical Pathology

Summaries of clinical chemistry tests are presented in Tables 7.1 - 7.44. Individual clinical chemistry data are in Appendix 6. Summaries of hematological tests are in presented in Tables 8.1 - 8.4. Individual hematology data are in Appendix 7. Individual urinalysis data are in Appendix 8.

WR238605-treatment produced changes in several clinical chemistry parameters suggesting a mild hepatotoxic affect. Significant increases in serum AST were seen in high dose males in Weeks 8 and 13, and in mid dose males in Week 8 (Table 7.3). A mild elevation in serum AST levels were also observed in high dose females in Week 13 (Table 7.4). Serum ALT levels were slightly but significantly increased in high dose males in Week 2 (Table 7.1). This was not seen at any other time point or in high dose females. Albumin decreases and/or reductions in albumin/globulin ratios were seen in Weeks 4 and 13 in high dose males and in Weeks 4, 8 and 13 in high dose females (Tables 7.7, 7.8, 7.11 and 7.12). Total protein levels, however, were not altered by treatment. Recovery from serum AST, ALT and albumin changes was evident by Week 18 (the first recovery period).

A significant increase in serum bilirubin levels was seen in high dose males but not females in Week 2 (Tables 7.13 and 7.14). This was supported by increased levels of bilirubin in the urine of these animals and in mid dose males in Week 4, although these latter animals did not demonstrate hyperbilirubinemia (Appendix 8).

Serum haptoglobin levels were below the limit of detection (< 13 mg/dl) on several occasions for control males and less frequently for low and mid dose males. Undetectable serum haptoglobin levels were frequently observed for females, especially for control and low dose females throughout the study. Consequently, these levels of serum haptoglobin below the limit of detection produced an apparent reduction in number of animals tested. Even so, significantly elevated serum haptoglobin levels were seen in high dose males and females in Weeks 4 and 8, and in mid dose males in Week 4 [Tables 7.43 and 7.44]. Biologically significant, but statistically insignificant increases in haptoglobin were seen in high dose animals in Week 13, and in mid dose males in Week 8 and mid dose females in Week 4. By the first recovery time point (Week 18), measurable haptoglobin levels were generally similar to control animal values. The occurrence of increased levels of this protein, which is synthesized by hepatocytes, is indicative of an inflammatory response, i.e. an acute phase reaction.

Significant methemoglobinemia was seen in high and mid dose animals throughout the treatment period (Tables 8.19 and 8.20). Methemoglobin levels generally remained constant during the treatment period. Recovery from methemoglobinemia occurred by the first recovery period (Week 18) in mid dose animals, but methemoglobin levels remained significantly elevated at that time in high dose animals. Methemoglobin levels

in high dose animals returned to levels seen in control animals by the end of the recovery period (Week 26).

Statistically significant reductions in RBC count were evident by Week 2 in high dose females and by Week 4 in high dose males and in mid dose animals (Tables 8.1 and 8.2). Corresponding decreases in hemoglobin levels and/or hematocrit occurred in these animals in Week 4 (Tables 8.3 - 8.6). Recovery was apparent, however, by Week 8. In high dose females, RBCs were anisocytotic in Weeks 2 and 4. Anisocytotic RBCs were observed in one high dose male in Week 2 and in one mid dose male in Week 4. In response to the anemic state, increased MCV was seen in high dose females and possibly males in Week 4 (Tables 8.7 and 8.8). These macrocytic RBCs were somewhat hypochromic (Tables 8.11 and 8.12), although their hemoglobin content (MCH) was similar to control animals (Tables 8.9 and 8.10). As with RBC count, these effects were no longer evident by Week 8. Compensatory responses to the anemic state included reticulocytosis in high dose animals (Weeks 4, 8 and 13) and in mid dose animals (Week 13; males and Weeks 4 and 8; females), as shown in Tables 8.13 and 8.14. An increased number of nucleated RBCs in high dose animals was also observed in Week 4 (Tables 8.15 and 8.16). Heinz bodies were not increased as a consequence of WR238605 treatment (Tables 8.17 and 8.18).

Mild to moderate thrombocytopenia was seen in Weeks 2 and 4 in high and to a somewhat lesser extent in mid dose animals (Tables 8.21 and 8.22). This was supported by the individual hematology morphology results (blood smears) in Appendix 7, which demonstrated marked to moderate decrease in platelet number in mid dose males (Weeks 2, 4, and 8); in high dose males (Weeks 2, 4, 8, and possibly 13); in mid dose females (Weeks 2, 4, and 8); and in high dose females (Weeks 2, 4, 8 and possibly 13). This was not apparent thereafter, nor was it seen in the low dose. The thrombocytopenia was accompanied primarily in high dose animals with a slight increase in platelet size, as estimated from blood smears (Appendix 7).

Prothrombin time was slightly reduced in both mid and high dose animals in Week 4 only (Tables 8.23 and 8.24), but activated partial thromboplastin time was unaffected by WR238605 treatment (Tables 8.23 and 8.24).

Leukocytosis was evident in high dose and to a lesser extent in mid dose males and possibly mid dose females primarily during the latter half of the treatment period (Tables 8.27 and 8.28). This leukocytosis was generally characterized by increased numbers of mature neutrophils and monocytes (Tables 8.29, 8.30, 8.35 and 8.36). In response, slight increases in immature neutrophils were also seen sporadically in mid and high dose females (Table 8.32) Complete reversal of the leukocytosis was apparent by Week 18.

Except for the previously described hyperbilirubinemia in mid and high dose males, urinalysis measurements were not affected by WR238605 treatment (Appendix 8).

No other clinical pathology changes appeared to be related to WR238605 treatment. Sporadic increases and decreases were seen, but were not considered biologically significant. Sporadic changes seen in high dose animals included a minimal but statistically significant elevation in serum triglycerides in high dose males but not females in Week 8 (Table 7.21) and slight decreases in inorganic phosphorus levels in high dose males in Week 2 (Table 7.39). As these changes were only seen once and in only one sex in the treatment period, they were not considered to be biologically significant.

4.6 Electrocardiography

The Cardiology Report is contained in Appendix 9. There were no significant ECG changes produced by WR238605 treatment. Any changes observed were considered incidental findings and not test article-related. Heart rate and PR and QT intervals were not affected by treatment.

4.7 Ophthalmology Examinations

The Ophthalmology Report is contained in Appendix 10.

In Week 13, one high dose female had congestion of the retinal vessels. This finding would be consistent with alterations in hematologic values (hemoglobin or hematocrit). The retinal congestion had resolved by Week 26. All other animals appeared similar to their baseline exam.

4.8 Organ Weights

Organ weight summaries for % body weight, % brain weight, and for absolute values are in Tables 9.1 - 9.4, 10.1 - 10.4 and 11.1 - 11.4, respectively. Individual organ weight data are contained in Appendix 11.

At the conclusion of treatment, significant increases in relative (% body weight) liver weights were seen in high dose males and high and mid dose females (Tables 9.1 and 9.2). Although not statistically significant the increased relative (% body weight) liver weights were considered biologically significant in mid dose males. These trends were also apparent when liver/brain weight ratios (% brain weight) and absolute liver weights were analyzed in males (Tables 10.1, 10.2, 11.1 and 11.2). Splenic weights were significantly increased in high dose animals. Splenic weights in mid dose animals were considered to be increased by a dose-related effect also. These changes (liver and splenic weights) were no longer seen at the end of the recovery period (Tables 10.3, 10.4, 11.3, 11.4, 12.3 and 12.4). No other organ weights were affected by WR238605 treatment. A statistically significant increase in relative and absolute thyroids-parathyroids weights were observed in mid and high dose males but not females at the end of the recovery period (Table 11.3). This result was not considered to be

biologically significant because these changes were not seen in these treatment groups at the end of the dosing period.

4.9 Pathology

The Pathology Report is contained in Appendix 12. A summary of microscopic lesions is shown in Table 12.

The oral administration of WR238605 in dogs was associated with histologic changes in the lungs, spleen, liver, thymus, and bone marrow. Several test article-related changes were observed in the lungs. Alveolar proteinosis was observed in mid and high dose animals at the end of the treatment period. This lesion was characterized by pale eosinophilic amphorous to fibrillar material in the alveoli, large discrete cells having abundant vacuolated cytoplasm in the alveolar and terminal bronchiolar lumen, and neutrophils present in the affected alveoli. Subacute inflammation consisting of macrophages and a few lymphocytes forming cuffs around venules and small arterioles was also seen at the end of the dosing period in a dose-related manner. This was apparent in mid and high dose animals and in low dose females. These two changes were considered to be direct test article-related changes. Alveolar proteinosis had completely resolved in males and almost resolved in females by the end of the recovery period. Resolution of subacute inflammation had progressed substantially as demonstrated by a decrease in the mean severity score. The process of resolution was obscured by the apparent spontaneous development of subacute inflammation observed in control and low dose animals by the end of the recovery period. However, the higher mean severity score in high dose animals as compared to controls suggests that the subacute inflammation had not been completely resolved. During the recovery period, chronic inflammation of the lungs developed. Chronic inflammation was seen as a focal or subcapsular change consisting of interstitial fibrosis, mononuclear cell infiltration, and sometimes hyperplasia of the alveolar or bronchiolar epithelium. This was interpreted as part of the process of alveolar proteinosis, and thus secondary to a direct treatment-related affect.

Treatment-related splenic lesions included extramedullary hematopoiesis and hemosiderin pigment in high dose and to a lesser extent in mid dose males and females. Hemosiderin pigment was also seen in one low dose male. All animals exhibited a recovery for extramedullary hematopoiesis. Absolute recovery from splenic hemosiderosis was masked by the spontaneous development of hemosiderosis in the control animals. Three control animals (two males and one female) which were sacrificed at the end of the recovery period spontaneously developed splenic hemosiderosis. This was not seen in control animals necropsied at the conclusion of treatment. However, the process of resolution of the splenic hemosiderosis was evident as judged by a reduction in the mean severity score. These splenic lesions were considered secondary changes caused by the clinical anemia produced by WR238605 treatment.

In the liver, hemosiderin deposits, Kupffer cell hypertrophy, and subacute inflammation occurred together in mid and high dose animals sacrificed at the end of the dosing period. Hemosiderin deposits and subacute inflammation of minimal severity also were each seen in a one low dose animals at that time. Hepatocellular necrosis of minimal severity was observed in high dose males. In animals sacrificed after the recovery period, Kupffer cell hypertrophy, subacute inflammation, and hepatocyte necrosis had completely resolved, but hemosiderin deposits persisted in mid dose and high dose animals. These changes were interpreted as consistent with the pathophysiologic response to a mild hemolytic anemia and its resolution following cessation of test article administration.

Another lesion interpreted as a secondary effect of WR238605-induced generalized toxicity or stress was depletion of thymic lymphocytes. This decrease in cortical lymphocytes varied from pale-staining with increased pyknotic lymphocytes to distinct thinning of the cortex. This lesion resolved by the end of the recovery period.

Bone marrow hypercellularity, in which hematopoietic cells replaced fat cells, was seen in all high dose animals and mid dose females. This was also observed in one mid and low dose male. Evaluation of bone marrow smears revealed a significant decrease in M:E ratios in mid and high dose animals. This decrease in M:E ratio was considered to be due to an increase in erythroid cells rather than a decrease in myeloid cells. These findings are consistent with observations of hemolytic anemia as evidenced by hemosiderin deposition in the liver and spleen, and thus was interpreted as a secondary effect of the erythrocyte destruction produced by drug treatment. The M:E ratio had recovered to normal by the end of the recovery period.

No other treatment-related histopathologic lesions were observed. As detailed in the Pathology Report (Appendix 12), a few organs were unavailable for microscopic examination. They were either inadvertently not collected at necropsy, lost in histologic processing or unavailable from sectioned (and re-sectioned) tissue. This included six mammary glands and four non-mammary gland tissues. Mammary gland tissue is often difficult to locate in appropriate male skin sections. None of these omissions was considered to have had an impact on the study as no treatment-related changes were seen in these missing tissues.

5. DISCUSSION

This study evaluated the toxicity of WR238605 in Beagle dogs following thirteen weeks of daily oral (gavage) administration. A thirteen week recovery period was included for all groups. The results are summarized in Table 1. None of the dogs died during the study. Generalized cyanosis manifested by blue tongue, gums and/or sclera was seen in all animals at the higher dose levels, and was supported by significant methemoglobinemia. Although barely perceptible blue tongue, gums and sclera were seen sporadicly in low dose animals, these observations were

not considered to be a biologically significant signs of cyanosis. Furthermore, elevations of methemoglobin levels were not observed in low dose animals. Body weight gains were decreased in high dose males and in mid and high dose females without a corresponding decrease in food consumption. In the recovery period, resolution of methemoglobinemia and the resulting cyanotic state was seen, and body weight gains were comparable among treatment groups.

Hemolytic anemia was observed at the high dose level and a lesser extent at the mid dose level. In Weeks 2 and/or 4, RBC count, hemoglobin level, and hematocrit were significantly lowered. MCHC was also decreased at the highest dose level. Compensatory physiologic responses included reticulocytosis and increased nucleated RBCs. Erythrocytes were anisocytotic in high dose females and to a lesser extent in mid and high dose males. Splenic extramedullary hematopoiesis and hemosiderosis in liver and spleen suggested that these "changes" were apparently secondary to hemolytic anemia. Although the anemic state was, in general, reversible after cessation of treatment, the secondary lesions such as hemosiderosis in liver and possibly the spleen were not completely resolved. Additional secondary responses to hemolytic anemia primarily seen in mid and high dose animals, included bone marrow hypercellularity supported by a decreased M:E ratio. These changes had resolved by the end of the recovery period. The aforementioned hematologic alterations including the methemoglobinemia may have been associated with the apparent congested retinal vessels in one high female seen at the conclusion of the treatment period. This had resolved at the end of the recovery period.

A significant dose-related increase in subacute inflammation in the lungs was seen in mid and high dose treatment groups at the end of the treatment period. Although subacute inflammation was observed in low dose animals, it was a low severity comparable to the spontaneous subacute inflammation observed in control animals at this time. Therefore, the biologic significance of the subacute inflammation observed in low dose animals is questionable. By the end of the recovery period, the lesions in the high dose animals were still in the process of resolution by the end of the recovery period as judged by a decrease in incidence and severity. Subacute inflammation in the lungs was judged to be a dose-related direct effect of WR238605 treatment.

Alveolar proteinosis occurred as another dose-related direct effect of WR238605-treatment in the lungs. The occurrence of alveolar proteinosis was limited to mid and high dose animals at the end of the treatment period. By the end of the recovery, alveolar proteinosis was still in the process of resolution as judged by a decrease in the incidence and severity. However, as part of the process of resolution of alveolar proteinosis, chronic inflammation of the alveolar and bronchiolar epithelium developed during the recovery period. The development of chronic inflammation was therefore judged to be a secondary treatment-related effect.

In the liver, hemosiderin deposits, Kupffer cell hypertrophy, and subacute inflammation primarily occurred in mid and high dose animals sacrificed at the end of the dosing period; although some of these changes were also seen in a few low dose animals at that time. In animals sacrificed after the recovery period, Kupffer cell hypertrophy had completely resolved, but hemosiderin deposits and subacute inflammation persisted in mid dose and high dose

animals. These changes were interpreted as consistent with the pathophysiologic response to a mild hemolytic anemia and its resolution following cessation of test article administration. Hepatocellular necrosis of minimal severity was observed in two high dose males. This could be correlated with the mild changes in AST, ALT, albumin, and A/G ratios in high dose males. Some of these clinical chemistry changes in the absence of supporting histopathology were also noted in mid dose animals. Significantly elevated serum haptoglobin levels, indicative of an acute phase reaction, may have been associated with the subacute inflammatory liver lesions noted in mid and high dose animals. All of these changes were reversible following cessation of treatment.

Indirect effects of WR238605 treatment possibly related to the stress included the depletion of thymic lymphocytes and the production of a neutrophilic and monocytic leukocytosis. These changes were limited to mid and high dose animals and were reversible upon cessation of treatment. A transient thrombocytopenia was also seen in high and mid dose animals. This decrease in platelet number was generally resolved by the end of the dosing period, and was not observed in the recovery period.

In an earlier four week oral (gavage) toxicity study of WR238605 (UIC/TRL Study No. 047), toxic effects similar to that seen in the present study were observed at dose levels of 16 and 6 mg base/kg/day. At these two higher doses, body weight loss in the absence of a reduction of food intake and cyanosis accompanied by methemoglobinemia were noted. Compensatory responses to the hypochromic anemia induced by drug treatment included reticulocytosis, increased levels of nucleated RBC's (high dose only), splenomegaly accompanied by extramedullary hematopoiesis and bone marrow hyperplasia. At these dose levels, mild hepatotoxicity was observed (alterations in A/G ratios and histologically, subacute hepatocellular inflammation). Subacute inflammation of the lungs accompanied by an alveolar macrophage response was also observed. While this lesion was observed in almost all of the animals, including control animals, the mean group severity at 6 and 16 mg base/kg/day was approximately two-fold higher than that seen in control and low dose (0.5 mg base/kg/day) animals. This inflammatory response involving the accumulation of alveolar macrophages might be a preface to the development of alveolar proteinosis seen in the present study. Additional effects seen in the one month study included thrombocytopenia (also seen in the present study), hypoglycemia and possible thymic lymphocyte depletion. Minimal toxicity was seen at the lowest dose level (0.5 mg base/kg/day) including signs of cyanosis with a statistically insignificant increase in methemoglobin production, and mild histologic changes in the bone marrow, liver, and possibly the spleen. On this basis, a no-observed effect level could not be determined.

As previously asserted, toxic effects similar to that observed in the one month study were apparent in the current thirteen week oral toxicity study of WR238605 which included a thirteen week recovery period. One significant direct treatment-related effect observed in this study and not in the four week oral toxicity study was the development of alveolar proteinosis. Also, chronic lung inflammation seen in recovery animals was considered to be the direct result of the process of resolution of this lesion. Alveolar proteinosis is a rare condition of unknown etiology. This lesion is characterized by the accumulation of granular, eosinophilic, periodic

acid-Schiff-positive protein-lipid material in the alveoli resembling pulmonary edema (Kairiman *et al.*, 1984). Common characteristics of alveolar proteinosis include changes in vascular permeability, abnormal increases in surfactant production and alterations in macrophage function (Boorman *et al.*, 1990; Claypool *et al.*, 1984). Although a variety of agents are capable of producing lung injury (Cooper, Jr. *et al.*, 1986a; Cooper, Jr. *et al.*, 1986b), the development of alveolar proteinosis has been primarily associated with exposure through inhalation (i.e. quartz and silica dust exposure and oxidant gases) (Rubin *et al.*, 1980, Corrin *et al.*, 1970; Dawkins *et al.*, 1991). Two pharmacologic agents which have been found to induce alveolar proteinosis are iprinodole (administered in diet), an anti-depressant drug, and chlorphentermine (administered intraperitoneally), an anoretic drug (Smith, 1980). Both compounds have been shown to produce alveolar proteinosis when administered chronically at large doses. In the present study, it is theorized that oxidative damage by the test article produced increased vascular permeability which allowed the leakage of amphorous to fibrillar eosinophilic material in the alveoli. The damage and resulting leakage of proteinaceous material resulted in the localization of neutrophils and alveolar macrophages to the site of injury. Although surfactant levels were not determined, changes observed in the present study are consistent with diagnosis of alveolar proteinosis.

As previously mentioned, the morphologic features of the chronic pulmonary inflammation observed in mid and high dose animals at the end of the recovery period suggested that it was produced as a result of the resolution of pulmonary alveolar proteinosis. As such, the chronic pulmonary inflammation was interpreted to be a secondary test article-related change. The chronic inflammation was of minimal to mild severity, and therefore would not be expected to have long-term effects on pulmonary function. However, longer term studies would be needed to confirm this.

In summary, the primary toxic effects of WR238605 included methemoglobinemia with clinical signs of cyanosis (blue gums, tongue, and sclera), decreased weight gain, apparent congested retinal vessels in one high dose female, hemolytic anemia, neutrophilic and monocytic leukocytosis, transient thrombocytopenia, pulmonary lesions (alveolar proteinosis and acute inflammation), bone marrow hypercellularity with an associated decreased M:E ratio, depletion of thymic lymphocytes and mild hepatotoxicity. These effects were generally seen at the high and mid dose levels, although hemosiderosis secondary to hemolytic anemia, and lung and bone marrow changes of minimal severity were also seen to a limited extent in low dose animals. These changes were essentially reversible, except for lung lesions and lesions secondary to the observed hemolytic anemia, e.g. hemosiderosis. Based upon the these findings, the no observed effect level in this study was equivocal, but was considered to be near the low dose level of 0.1 mg base/kg/day.

6. PERSONNEL

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Quality Assurance	Ronald Schoenbeck

Report preparation was assisted by Drs. E. Marianna Furedi-Machacek and Clyde W. Wheeler.

7. ARCHIVES

The raw data, specimens, test article reserves, and final report are archived at the Toxicology Research Laboratory (TRL), University of Illinois at Chicago (UIC), Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

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Table 1
THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

Summary of Toxic Responses

Dose (mg base/kg/day)	0	0.1	2.0	6.0
Dogs/Sex	4 + 4[a]	4 + 4[a]	4 + 4[a]	4 + 4[a]
Deaths	0	0	0	0
Body Weight Gain	-	NE	↓ (M) ↓ (F)	↓ (M) ↓ (F)
Food Consumption	-	NE	NE	NE
Clinical Signs	-	Blue tongue (sporadic) Blue sclera (sporadic)	Blue tongue Blue sclera Blue gums	Blue tongue Blue sclera Blue gums
Hematology[b]	-	NE	↑ METHGB ↓ RBC ↓ HGB ↓ MCHC (M) ↑ RETIC ↓ PLT ↓ PT ↑ WBC (M) ↑ MNEUT (M) ↑ INEUT (F) ↑ MON	↑ METHGB ↓ RBC ↓ HGB ↓ HCT ↓ MCHC ↑ MCV (F) (M?) ↑ RETIC ↑ NRBC ↓ PLT ↓ PT ↑ WBC ↑ MNEUT ↑ INEUT (F) ↑ MON
Clinical Chemistry[c]	-	NE	↑ AST ↑ HPT (M) (F ?)	↑ ALT (M ?) ↑ AST ↓ ALB ↓ A/G ↑ TRY (M) ↑ HPT ↑ BILI (M)
Urinalysis	-	NE	BILI (M ?)	BILI (M ?)
Electrocardiography	-	NE	NE	-
Ophthalmology	-	NE	NE	Congested retinal vessels (1F)
Organ Weights	-	NE	↑ Spleen (?) ↑ Liver	↑ Spleen ↑ Liver
Histopathology	Lungs - subacute inflammation	Lungs - subacute inflammation Spleen - hemosiderin pigment (M) Liver - hemosiderin pigment (F) subacute inflammation (M) Bone marrow - hypercellularity (M)	Lungs - alveolar proteinosis subacute inflammation Spleen - extramedullary hematopoiesis hemosiderin pigment Liver - hemosiderin pigment Kupffer cell hypertrophy subacute inflammation Thymus - lymphocyte depletion (F) Bone marrow - hypercellularity ↓ M/E Ratio	Lungs - alveolar proteinosis subacute inflammation Spleen - extramedullary hematopoiesis hemosiderin pigment Liver - hemosiderin pigment Kupffer cell hypertrophy subacute inflammation hepatocyte necrosis (M) Thymus - lymphocyte depletion Bone marrow - hypercellularity ↓ M/E Ratio
Recovery Period	Essentially complete recovery occurred at the end of the 13 week recovery period. The exceptions were incomplete resolution of alveolar proteinosis, pulmonary subacute inflammation, and splenic and hepatic lesions secondary to the hemolytic anemia. Also as part of the resolution of alveolar proteinosis, chronic inflammation developed in the lungs. However, pulmonary subacute (M + F) and chronic (1F) inflammation, and hepatic hemosiderin pigmentation were seen in control animals.			
CONCLUSIONS	The primary toxic affects were seen in the lungs, RBCs, and liver. Significant methemoglobin production was observed in mid and high dose animals, but was reversible. Microscopic lesions in the spleen, liver and bone marrow were secondary to mild hemolytic anemia, although hepatocyte necrosis in high dose males supported by clinical chemisty changes was also noted. Transient thrombocytopenia and the depletion of thymic lymphocytes were observed at the higher dose levels. Toxicity was primarily limited to the two highest dose levels, although limited toxicity was seen in the lowest dose tested.			

[a]Recovery animals.

[b]METHGB = methemoglobin, RBC = erythrocytes, HGB = hemoglobin, HCT = hematocrit, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MCHC = mean corpuscular hemoglobin concentration, RETIC = reticulocytes, PLT = platelets, PT = prothrombin time, WBC = leukocytes, MNEUT = mature neutrophils, INEUT = immature neutrophils, MON = monocytes

[c]ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALB = albumin, A/G = albumin/globulin ratio, HPT = haptoglobin, TRY = triglycerides.

? = Possible or marginal effect NE = No effect

Table 2

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

Dosage Formulation Analyses[a]

Target Concentration (mg base/ml)	Weeks 1/2	% Target	Weeks 7/8	% Target	Week 13	% Target
0	0.00	----	0.00	----	----	----
0.1	0.097 ± 0.002	97.0	0.097 ± 0.001	97.0	0.105 ± 0.007	105.0
0.2	1.978 ± 0.031	98.9	1.930 ± 0.008	96.5	1.969 ± 0.048	98.4
6.0	5.479 ± 0.149	91.3	6.306 ± 0.017	105.1	6.457 ± 0.023	107.6

[a]Mean ± standard deviation for triplicate runs.

Table 3

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL SIGNS

STUDY: 097 SEX: MALE

DOSE:(mg/kg)	0	0.1	2.0	6.0 mg base/kg/day
GROUP:	1M	2M	3M	4M
TREATMENT PERIOD				
Scheduled Sacrifice	4	4	4	4
Blue Gums	0	0	8	8
Blue Tongue	0	1	8	8
Dehydrated	0	0	0	2
Blue Sclera	0	2	8	8
Total Number of Animals	8	8	8	8
RECOVERY PERIOD				
Scheduled Sacrifice	4	4	4	4
Blue Gums	0	0	2	3
Blue Tongue	0	1	4	4
Blue Sclera	0	1	4	4
Total Number of Animals	4	4	4	4

STUDY: 097 SEX: FEMALE

DOSE:(mg/kg)	0	0.1	2.0	6.0 mg base/kg/day
GROUP:	1F	2F	3F	4F
TREATMENT PERIOD				
Scheduled Sacrifice	4	4	4	4
Blue Gums	0	1	8	8
Blue Tongue	0	4	8	8
Dehydrated	0	0	0	1
Blue Sclera	0	5	7	8
Total Number of Animals	8	8	8	8
RECOVERY PERIOD				
Scheduled Sacrifice	4	4	4	4
Blue Gums	0	0	4	4
Blue Tongue	0	2	4	4
Blue Sclera	0	2	4	4
Total Number of Animals	4	4	4	4

Table 4.1

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 097 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1M	0.1 2M	2.0 3M	6.0 4M	mg base/kg/day
TREATMENT PERIOD						
DAY -8	MEAN	10.5	10.4	10.6	10.4	
	S.D.	0.51	0.44	0.58	0.35	
	N	8	8	8	8	
DAY 0	MEAN	10.3	10.2	10.4	10.2	
	S.D.	0.54	0.47	0.35	0.32	
	N	8	8	8	8	
DAY 7	MEAN	10.6	10.4	10.4	10.4	
	S.D.	0.52	0.47	0.41	0.33	
	N	8	8	8	8	
DAY 13	MEAN	10.5	10.3	10.4	10.2	
	S.D.	0.56	0.45	0.37	0.41	
	N	8	8	8	8	
DAY 21	MEAN	10.7	10.6	10.5	10.2	
	S.D.	0.59	0.44	0.41	0.41	
	N	8	8	8	8	
DAY 28	MEAN	10.7	10.6	10.4	10.1*	
	S.D.	0.49	0.50	0.38	0.38	
	N	8	8	8	8	
DAY 35	MEAN	11.1	10.8	10.6	10.2*	
	S.D.	0.46	0.44	0.36	0.40	
	N	8	8	8	8	
DAY 42	MEAN	10.9	10.6	10.5	10.0*	
	S.D.	0.52	0.46	0.51	0.61	
	N	8	8	8	8	
DAY 49	MEAN	11.1	10.9	10.7	10.1*	
	S.D.	0.54	0.53	0.49	0.48	
	N	8	8	8	8	
DAY 56	MEAN	11.0	10.7	10.5	9.8*	
	S.D.	0.53	0.47	0.55	0.67	
	N	8	8	8	8	
DAY 63	MEAN	11.1	10.8	10.6	9.9*	
	S.D.	0.56	0.49	0.55	0.77	
	N	8	8	8	8	
DAY 70	MEAN	11.1	10.9	10.7	9.9*	
	S.D.	0.49	0.52	0.58	0.71	
	N	8	8	8	8	
DAY 77	MEAN	11.1	10.8	10.7	9.8*	
	S.D.	0.48	0.47	0.65	0.88	
	N	8	8	8	8	
DAY 84	MEAN	11.1	10.9	10.7	9.8*	
	S.D.	0.49	0.48	0.74	0.89	
	N	8	8	8	8	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 4.2

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 097 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1F	0.1 2F	2.0 3F	6.0 4F	mg base/kg/day
TREATMENT PERIOD						
DAY -8	MEAN	8.7	8.8	9.0	9.0	
	S.D.	0.91	0.69	0.91	0.70	
	N	8	8	8	8	
DAY 0	MEAN	8.6	8.7	8.8	8.9	
	S.D.	0.84	0.63	0.80	0.78	
	N	8	8	8	8	
DAY 7	MEAN	8.8	8.9	8.9	8.9	
	S.D.	0.86	0.71	0.87	0.82	
	N	8	8	8	8	
DAY 13	MEAN	8.7	8.8	8.7	8.8	
	S.D.	0.86	0.69	0.87	0.89	
	N	8	8	8	8	
DAY 21	MEAN	8.9	9.1	8.7	8.6	
	S.D.	0.84	0.72	0.93	0.92	
	N	8	8	8	8	
DAY 28	MEAN	9.0	9.0	8.6	8.6	
	S.D.	0.82	0.71	0.94	0.91	
	N	8	8	8	8	
DAY 35	MEAN	9.2	9.3	8.7	8.7	
	S.D.	0.86	0.83	0.98	0.93	
	N	8	8	8	8	
DAY 42	MEAN	9.2	9.1	8.6	8.7	
	S.D.	0.86	0.80	0.93	0.86	
	N	8	8	8	8	
DAY 49	MEAN	9.4	9.4	8.7	8.8	
	S.D.	0.96	0.92	0.92	0.82	
	N	8	8	8	8	
DAY 56	MEAN	9.3	9.2	8.5	8.6	
	S.D.	0.90	1.05	0.97	0.88	
	N	8	8	8	8	
DAY 63	MEAN	9.4	9.2	8.7	8.7	
	S.D.	0.96	1.04	1.11	0.82	
	N	8	8	8	8	
DAY 70	MEAN	9.6	9.3	8.6	8.7	
	S.D.	0.93	1.01	1.12	0.74	
	N	8	8	8	8	
DAY 77	MEAN	9.6	9.2	8.7	8.7	
	S.D.	1.00	1.05	1.17	0.79	
	N	8	8	8	8	
DAY 84	MEAN	9.6	9.3	8.7	8.7	
	S.D.	1.01	1.02	1.23	0.71	
	N	8	8	8	8	

Analysis of Variance using DUNNETT'S Procedure

Table 4.3

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 097 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1M	0.1 2M	2.0 3M	6.0 4M	mg base/kg/day
RECOVERY PERIOD						
DAY 91	MEAN	11.1	11.0	10.7	10.0	
	S.D.	0.57	0.28	0.62	0.57	
	N	4	4	4	4	
DAY 98	MEAN	11.1	10.7	10.6	9.9	
	S.D.	0.67	0.39	0.78	0.66	
	N	4	4	4	4	
DAY 105	MEAN	11.0	10.7	10.6	9.9	
	S.D.	0.67	0.44	0.80	0.59	
	N	4	4	4	4	
DAY 112	MEAN	11.2	10.8	10.8	10.0	
	S.D.	0.68	0.52	0.81	0.64	
	N	4	4	4	4	
DAY 119	MEAN	11.4	11.1	11.2	10.3	
	S.D.	0.65	0.68	0.80	0.54	
	N	4	4	4	4	
DAY 126	MEAN	11.3	10.9	11.1	10.2	
	S.D.	0.64	0.68	0.74	0.56	
	N	4	4	4	4	
DAY 133	MEAN	11.6	11.5	11.5	10.7	
	S.D.	0.44	0.90	0.62	0.62	
	N	4	4	4	4	
DAY 140	MEAN	11.6	11.1	11.3	10.3	
	S.D.	0.69	0.97	0.88	0.68	
	N	4	4	4	4	
DAY 147	MEAN	11.5	11.0	11.1	10.5	
	S.D.	0.63	1.05	0.80	0.70	
	N	4	4	4	4	
DAY 154	MEAN	11.7	11.1	11.2	10.4	
	S.D.	0.68	1.18	0.93	0.67	
	N	4	4	4	4	
DAY 161	MEAN	11.9	11.3	11.3	10.6	
	S.D.	0.70	1.10	0.94	0.64	
	N	4	4	4	4	
DAY 168	MEAN	12.1	11.8	11.9	11.3	
	S.D.	0.47	0.78	0.67	0.80	
	N	4	4	4	4	
DAY 175	MEAN	12.0	11.7	11.7	11.1	
	S.D.	0.92	0.70	0.74	0.62	
	N	4	4	4	4	

Analysis of Variance using DUNNETT'S Procedure

Table 4.4

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 097 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1F	0.1 2F	2.0 3F	6.0 4F	mg base/kg/day
RECOVERY PERIOD						
DAY 91	MEAN	9.9	9.6	8.4	8.6	
	S.D.	1.14	0.68	0.75	0.35	
	N	4	4	4	4	
DAY 98	MEAN	9.9	9.4	8.5	8.6	
	S.D.	1.13	0.64	0.65	0.32	
	N	4	4	4	4	
DAY 105	MEAN	9.8	9.5	8.8	8.7	
	S.D.	1.17	0.66	0.86	0.42	
	N	4	4	4	4	
DAY 112	MEAN	9.9	9.4	9.0	8.9	
	S.D.	1.31	0.53	0.92	0.48	
	N	4	4	4	4	
DAY 119	MEAN	10.1	9.6	9.0	9.1	
	S.D.	1.47	0.47	0.88	0.42	
	N	4	4	4	4	
DAY 126	MEAN	9.9	9.5	8.9	9.1	
	S.D.	1.40	0.50	0.76	0.53	
	N	4	4	4	4	
DAY 133	MEAN	10.1	9.9	9.1	9.3	
	S.D.	1.24	0.78	0.49	0.67	
	N	4	4	4	4	
DAY 140	MEAN	10.1	9.8	9.1	9.4	
	S.D.	1.31	0.54	0.74	0.65	
	N	4	4	4	4	
DAY 147	MEAN	10.1	9.8	9.2	9.3	
	S.D.	1.34	0.56	0.82	0.61	
	N	4	4	4	4	
DAY 154	MEAN	10.2	9.6	9.2	9.3	
	S.D.	1.40	0.69	0.83	0.67	
	N	4	4	4	4	
DAY 161	MEAN	10.2	10.0	9.1	9.3	
	S.D.	1.44	0.37	0.86	0.89	
	N	4	4	4	4	
DAY 168	MEAN	10.4	10.5	9.4	9.8	
	S.D.	1.36	0.37	0.73	1.18	
	N	4	4	4	4	
DAY 175	MEAN	10.5	10.8	9.5	9.9	
	S.D.	1.32	0.53	0.85	1.17	
	N	4	4	4	4	

Analysis of Variance using DUNNETT'S Procedure

Table 5.1

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 097 SEX: MALE

PERIOD[a]	DOSE: (mg/kg) GROUP:	0 1M	0.1 2M	2.0 3M	6.0 4M	mg base/kg/day
TREATMENT PERIOD						
DAY 7[b]	MEAN	0.3	0.2	0.1*	0.1*	
	S.D.	0.12	0.14	0.11	0.13	
	N	8	8	8	8	
DAY 13	MEAN	-0.2	-0.1	-0.1	-0.2	
	S.D.	0.12	0.18	0.16	0.16	
	N	8	8	8	8	
DAY 21	MEAN	0.3	0.3	0.2	0.0*	
	S.D.	0.16	0.24	0.14	0.15	
	N	8	8	8	8	
DAY 28	MEAN	0.0	0.0	-0.2	-0.1	
	S.D.	0.15	0.20	0.20	0.16	
	N	8	8	8	8	
DAY 35	MEAN	0.3	0.2	0.2	0.1*	
	S.D.	0.07	0.15	0.18	0.17	
	N	8	8	8	8	
DAY 42	MEAN	-0.1	-0.1	-0.1	-0.2	
	S.D.	0.24	0.21	0.25	0.31	
	N	8	8	8	8	
DAY 49	MEAN	0.2	0.3	0.2	0.1	
	S.D.	0.14	0.24	0.28	0.24	
	N	8	8	8	8	
DAY 56	MEAN	-0.1	-0.2	-0.3	-0.3	
	S.D.	0.28	0.20	0.29	0.30	
	N	8	8	8	8	
DAY 63	MEAN	0.1	0.1	0.1	0.1	
	S.D.	0.11	0.14	0.07	0.14	
	N	8	8	8	8	
DAY 70	MEAN	0.0	0.1	0.1	-0.1	
	S.D.	0.20	0.15	0.15	0.26	
	N	8	8	8	8	
DAY 77	MEAN	0.0	0.0	0.0	-0.1	
	S.D.	0.07	0.16	0.19	0.22	
	N	8	8	8	8	
DAY 84	MEAN	0.0	0.1	0.0	0.0	
	S.D.	0.19	0.09	0.22	0.07	
	N	8	8	8	8	
TOTAL GAIN	MEAN	0.8	0.7	0.3	-0.4*	
	S.D.	0.32	0.34	0.60	0.70	
	N	8	8	8	8	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a] Successive periods
[b] Baseline is Day 0

Table 5.2

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 097 SEX: FEMALE

PERIOD[a]	DOSE: (mg/kg) GROUP:	0 1F	0.1 2F	2.0 3F	6.0 4F	mg base/kg/day
TREATMENT PERIOD						
DAY 7[b]	MEAN	0.2	0.2	0.1	0.0	
	S.D.	0.19	0.11	0.17	0.07	
	N	8	8	8	8	
DAY 13	MEAN	-0.1	0.0	-0.2	-0.2	
	S.D.	0.18	0.10	0.18	0.12	
	N	8	8	8	8	
DAY 21	MEAN	0.2	0.3	0.0	-0.1*	
	S.D.	0.11	0.13	0.19	0.23	
	N	8	8	8	8	
DAY 28	MEAN	0.1	-0.1	-0.1*	-0.1	
	S.D.	0.13	0.13	0.05	0.20	
	N	8	8	8	8	
DAY 35	MEAN	0.3	0.2	0.1	0.1	
	S.D.	0.21	0.21	0.20	0.11	
	N	8	8	8	8	
DAY 42	MEAN	0.0	-0.2	-0.1	0.1	
	S.D.	0.15	0.21	0.14	0.18	
	N	8	8	8	8	
DAY 49	MEAN	0.2	0.3	0.2	0.1	
	S.D.	0.20	0.22	0.11	0.10	
	N	8	8	8	8	
DAY 56	MEAN	-0.1	-0.2	-0.2	-0.2	
	S.D.	0.18	0.25	0.23	0.15	
	N	8	8	8	8	
DAY 63	MEAN	0.1	0.1	0.2	0.1	
	S.D.	0.11	0.16	0.21	0.24	
	N	8	8	8	8	
DAY 70	MEAN	0.2	0.1	-0.1	-0.1	
	S.D.	0.24	0.27	0.18	0.18	
	N	8	8	8	8	
DAY 77	MEAN	0.1	-0.1	0.0	0.0	
	S.D.	0.16	0.19	0.19	0.11	
	N	8	8	8	8	
DAY 84	MEAN	0.0	0.0	0.0	0.0	
	S.D.	0.14	0.18	0.12	0.33	
	N	8	8	8	8	
TOTAL GAIN	MEAN	1.1	0.6	-0.2*	-0.2*	
	S.D.	0.42	0.87	0.98	0.57	
	N	8	8	8	8	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a] Successive periods
[b] Baseline is Day 0

Table 5.3

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 097 SEX: MALE

PERIOD[a]	DOSE: (mg/kg) GROUP:	0 1M	0.1 2M	2.0 3M	6.0 4M	mg base/kg/day
RECOVERY PERIOD						
DAY 91	MEAN	0.1	0.4	0.0	0.2	
	S.D.	0.17	0.13	0.29	0.33	
	N	4	4	4	4	
DAY 98	MEAN	0.0	-0.3	-0.1	-0.2	
	S.D.	0.29	0.12	0.22	0.13	
	N	4	4	4	4	
DAY 105	MEAN	-0.1	0.0	0.0	0.0	
	S.D.	0.14	0.08	0.22	0.13	
	N	4	4	4	4	
DAY 112	MEAN	0.2	0.1	0.2	0.1	
	S.D.	0.05	0.13	0.05	0.15	
	N	4	4	4	4	
DAY 119	MEAN	0.2	0.3	0.3	0.3	
	S.D.	0.06	0.17	0.05	0.15	
	N	4	4	4	4	
DAY 126	MEAN	-0.1	-0.2	-0.1	0.0	
	S.D.	0.10	0.08	0.14	0.10	
	N	4	4	4	4	
DAY 133	MEAN	0.3	0.6	0.4	0.5	
	S.D.	0.22	0.22	0.21	0.14	
	N	4	4	4	4	
DAY 140	MEAN	0.0	-0.4	-0.2	-0.4	
	S.D.	0.29	0.08	0.45	0.32	
	N	4	4	4	4	
DAY 147	MEAN	-0.1	-0.1	-0.2	0.2	
	S.D.	0.17	0.10	0.13	0.17	
	N	4	4	4	4	
DAY 154	MEAN	0.1	0.1	0.1	-0.1	
	S.D.	0.10	0.24	0.22	0.25	
	N	4	4	4	4	
DAY 161	MEAN	0.2	0.2	0.1	0.2	
	S.D.	0.18	0.14	0.22	0.10	
	N	4	4	4	4	
DAY 168	MEAN	0.3	0.5	0.6	0.7	
	S.D.	0.25	0.33	0.47	0.39	
	N	4	4	4	4	
DAY 175	MEAN	-0.1	-0.1	-0.2	-0.2	
	S.D.	0.56	0.25	0.10	0.22	
	N	4	4	4	4	
TOTAL GAIN	MEAN	0.9	1.1	1.1	1.3	
	S.D.	0.49	0.44	0.26	0.41	
	N	4	4	4	4	

Analysis of Variance using DUNNETT'S Procedure

[a]Successive periods

Table 5.4

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 097 SEX: FEMALE

PERIOD[a]	DOSE: (mg/kg) GROUP:	0 1F	0.1 2F	2.0 3F	6.0 4F	mg base/kg/day
RECOVERY PERIOD						
DAY 91	MEAN	0.1	0.0	-0.1	0.0	
	S.D.	0.05	0.29	0.24	0.17	
	N	4	4	4	4	
DAY 98	MEAN	0.0	-0.2	0.1	0.1	
	S.D.	0.24	0.25	0.15	0.13	
	N	4	4	4	4	
DAY 105	MEAN	-0.1	0.0	0.3*	0.1	
	S.D.	0.06	0.19	0.22	0.12	
	N	4	4	4	4	
DAY 112	MEAN	0.1	-0.1	0.1	0.2	
	S.D.	0.17	0.28	0.13	0.14	
	N	4	4	4	4	
DAY 119	MEAN	0.2	0.2	0.1	0.2	
	S.D.	0.17	0.18	0.06	0.22	
	N	4	4	4	4	
DAY 126	MEAN	-0.2	-0.1	-0.1	-0.1	
	S.D.	0.08	0.06	0.19	0.24	
	N	4	4	4	4	
DAY 133	MEAN	0.2	0.4	0.3	0.3	
	S.D.	0.34	0.32	0.30	0.28	
	N	4	4	4	4	
DAY 140	MEAN	0.1	-0.1	-0.1	0.1	
	S.D.	0.15	0.27	0.26	0.05	
	N	4	4	4	4	
DAY 147	MEAN	-0.1	0.0	0.1	-0.1	
	S.D.	0.21	0.12	0.15	0.10	
	N	4	4	4	4	
DAY 154	MEAN	0.1	-0.2	-0.1	0.0	
	S.D.	0.22	0.14	0.21	0.15	
	N	4	4	4	4	
DAY 161	MEAN	0.0	0.4	0.0	0.0	
	S.D.	0.13	0.41	0.13	0.29	
	N	4	4	4	4	
DAY 168	MEAN	0.2	0.5	0.3	0.5	
	S.D.	0.15	0.21	0.49	0.34	
	N	4	4	4	4	
DAY 175	MEAN	0.1	0.3	0.1	0.2	
	S.D.	0.19	0.47	0.12	0.10	
	N	4	4	4	4	
TOTAL GAIN	MEAN	0.8	1.2	1.0	1.3	
	S.D.	0.26	1.34	0.82	1.03	
	N	4	4	4	4	

Analysis of Variance using DUNNETT'S Procedure

[a]Successive periods

Table 6.1

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 097 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1M	0.1 2M	2.0 3M	6.0 4M	mg base/kg/day
			TREATMENT PERIOD			
DAY -14	INTAKE (g)	328	277	281	292	
	S.D.	65.4	86.9	91.1	76.4	
	N	8	8	8	8	
DAY -8	INTAKE (g)	319	335	293	309	
	S.D.	76.2	88.4	85.9	58.8	
	N	8	8	8	8	
DAY 6	INTAKE (g)	360	335	314	352	
	S.D.	44.8	73.8	78.8	59.2	
	N	7	8	8	8	
DAY 9	INTAKE (g)	332	369	324	343	
	S.D.	92.2	34.0	68.4	61.8	
	N	8	8	8	8	
DAY 20	INTAKE (g)	396	381	310	315	
	S.D.	11.3	48.7	92.2	63.0	
	N	8	8	8	8	
DAY 23	INTAKE (g)	400	389	350	361	
	S.D.	0.4	19.7	46.1	57.1	
	N	8	8	8	8	
DAY 34	INTAKE (g)	400	378	341	363	
	S.D.	0.0	35.4	79.7	42.4	
	N	8	8	8	8	
DAY 41	INTAKE (g)	400	400	397	398	
	S.D.	0.0	0.0	8.8	4.1	
	N	8	8	8	8	
DAY 48	INTAKE (g)	400	383	388	366	
	S.D.	0.0	47.7	21.6	64.8	
	N	8	8	8	8	
DAY 51	INTAKE (g)	400	387	387	386	
	S.D.	0.0	36.1	23.3	38.1	
	N	8	8	8	8	
DAY 62	INTAKE (g)	400	385	370	400	
	S.D.	0.0	27.0	56.2	0.0	
	N	8	8	8	8	
DAY 69	INTAKE (g)	400	400	400	397	
	S.D.	0.0	0.0	0.0	9.2	
	N	8	8	8	8	
DAY 77	INTAKE (g)	400	395	395	400	
	S.D.	0.0	14.8	13.4	0.0	
	N	8	8	8	8	
DAY 83	INTAKE (g)	400	391	370	397	
	S.D.	0.0	25.8	60.1	8.1	
	N	8	8	8	8	
DAY 86	INTAKE (g)	400	400	346	400	
	S.D.	0.0	0.0	77.4	0.0	
	N	8	3	3	3	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 097 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1F	0.1 2F	2.0 3F	6.0 4F	mg base/kg/day
		TREATMENT PERIOD				
DAY -14	INTAKE (g)	225	232	203	213	
	S.D.	80.0	76.0	44.5	41.0	
	N	8	8	8	8	
DAY -8	INTAKE (g)	263	237	256	234	
	S.D.	88.3	91.4	57.8	70.3	
	N	8	8	8	8	
DAY 6	INTAKE (g)	303	266	261	239	
	S.D.	71.8	100.6	71.4	69.7	
	N	8	8	8	8	
DAY 9	INTAKE (g)	285	297	253	226	
	S.D.	94.1	72.8	62.6	61.9	
	N	8	8	8	8	
DAY 20	INTAKE (g)	305	312	298	265	
	S.D.	85.2	81.9	77.1	123.5	
	N	8	8	8	8	
DAY 23	INTAKE (g)	337	325	255	239	
	S.D.	67.1	81.6	94.6	88.4	
	N	8	8	8	8	
DAY 34	INTAKE (g)	303	354	302	276	
	S.D.	96.2	55.3	74.8	58.8	
	N	8	8	8	8	
DAY 41	INTAKE (g)	358	355	339	321	
	S.D.	73.4	59.1	87.6	64.1	
	N	8	8	8	8	
DAY 48	INTAKE (g)	376	334	335	287	
	S.D.	46.0	78.5	79.1	101.1	
	N	8	8	8	8	
DAY 51	INTAKE (g)	318	344	345	256	
	S.D.	96.6	78.5	52.6	83.0	
	N	8	8	8	8	
DAY 62	INTAKE (g)	329	351	375	272	
	S.D.	89.8	52.7	36.9	105.6	
	N	8	8	8	8	
DAY 69	INTAKE (g)	380	365	367	293	
	S.D.	40.8	59.5	47.7	82.3	
	N	8	8	8	8	
DAY 77	INTAKE (g)	381	333	366	322	
	S.D.	36.9	114.9	73.7	66.3	
	N	8	8	8	8	
DAY 83	INTAKE (g)	392	355	359	279	
	S.D.	23.3	84.1	88.8	109.7	
	N	8	8	8	8	
DAY 86	INTAKE (g)	376	320	324	288	
	S.D.	44.9	104.5	104.2	94.3	
	N	8	8	8	8	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 097 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1M	0.1 2M	2.0 3M	6.0 4M	mg base/kg/day
RECOVERY PERIOD						
DAY 97	INTAKE (g)	375	400	394	400	
	S.D.	50.0	0.0	12.5	0.0	
	N	4	4	4	4	
DAY 104	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 111	INTAKE (g)	386	400	400	400	
	S.D.	28.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 118	INTAKE (g)	395	400	400	400	
	S.D.	9.5	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 121	INTAKE (g)	392	400	373	400	
	S.D.	15.5	0.0	55.0	0.0	
	N	4	4	4	4	
DAY 132	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 139	INTAKE (g)	373	400	382	400	
	S.D.	54.5	0.0	37.0	0.0	
	N	4	4	4	4	
DAY 146	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 153	INTAKE (g)	367	400	400	400	
	S.D.	66.5	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 160	INTAKE (g)	321	400	400	400	
	S.D.	110.3	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 167	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 174	INTAKE (g)	318	400	368	400	
	S.D.	123.5	0.0	64.5	0.0	
	N	4	4	4	4	
DAY 177	INTAKE (g)	348	337	400	400	
	S.D.	68.7	82.6	0.0	0.0	
	N	4	4	4	4	

Table 6.4

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY
OF WR 238605 WITH A THIRTEEN WEEK
RECOVERY PERIOD IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 097 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1F	0.1 2F	2.0 3F	6.0 4F	mg base/kg/day
RECOVERY PERIOD						
DAY 97	INTAKE (g)	351	346	347	337	
	S.D.	57.4	108.5	72.7	88.1	
	N	4	4	4	4	
DAY 104	INTAKE (g)	334	300	400	374	
	S.D.	76.5	121.2	0.0	51.5	
	N	4	4	4	4	
DAY 111	INTAKE (g)	332	321	360	330	
	S.D.	89.0	122.0	31.9	83.0	
	N	4	4	4	4	
DAY 118	INTAKE (g)	339	339	312	310	
	S.D.	47.5	89.2	69.4	75.9	
	N	4	4	4	4	
DAY 121	INTAKE (g)	357	362	327	338	
	S.D.	54.3	75.5	93.5	81.0	
	N	4	4	4	4	
DAY 132	INTAKE (g)	334	366	335	353	
	S.D.	78.9	68.0	47.1	93.5	
	N	4	4	4	4	
DAY 139	INTAKE (g)	351	380	298	326	
	S.D.	50.0	41.0	78.4	88.8	
	N	4	4	4	4	
DAY 146	INTAKE (g)	338	377	304	392	
	S.D.	94.1	46.5	98.7	16.0	
	N	4	4	4	4	
DAY 153	INTAKE (g)	362	341	287	336	
	S.D.	60.6	82.0	87.5	84.8	
	N	4	4	4	4	
DAY 160	INTAKE (g)	352	381	285	346	
	S.D.	38.9	23.3	93.8	64.1	
	N	4	4	4	4	
DAY 167	INTAKE (g)	316	372	323	378	
	S.D.	98.9	57.0	86.5	27.1	
	N	4	4	4	4	
DAY 174	INTAKE (g)	311	341	269	341	
	S.D.	114.6	78.6	125.8	118.5	
	N	4	4	4	4	
DAY 177	INTAKE (g)	330	346	271	379	
	S.D.	78.0	41.1	89.1	42.5	
	N	4	4	4	4	

Table 7.1

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alanine Aminotransferase

STUDY ID: 097
STUDY NO: 097
ABBR: ALT

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	36	38	38	45	
SD	12.5	6.0	8.3	11.8	
N	8	8	8	8	
Period: Week -1					
MEAN	30	30	33	38	
SD	9.1	6.3	6.1	9.1	
N	8	8	8	8	
Period: Week 2					
MEAN	28	36	34	44*	
SD	7.8	5.7	6.1	7.3	
N	8	8	8	8	
Period: Week 4					
MEAN	31	39	30	35	
SD	10.1	9.8	5.2	7.9	
N	8	8	8	8	
Period: Week 8					
MEAN	33	45	36	43	
SD	9.4	24.9	6.0	6.3	
N	8	8	8	8	
Period: Week 13					
MEAN	35	43	40	40	
SD	8.6	12.3	11.3	6.3	
N	8	8	8	8	
Period: Week 18					
MEAN	34	41	42	46	
SD	8.5	8.0	5.8	5.6	
N	4	4	4	4	
Period: Week 26					
MEAN	35	40	41	46	
SD	9.5	9.5	3.4	8.6	
N	4	4	4	4	

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alanine Aminotransferase

STUDY ID: 097
STUDY NO: 097
ABBR: ALT

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	36	36	33	35
SD	4.8	4.9	6.5	4.6
N	8	8	8	8
Period: Week -1				
MEAN	29	30	30	29
SD	5.7	5.9	4.7	4.1
N	8	8	8	8
Period: Week 2				
MEAN	31	32	30	28
SD	2.4	5.6	10.0	3.6
N	8	8	8	8
Period: Week 4				
MEAN	31	34	38	21
SD	2.5	6.6	24.6	3.4
N	8	8	8	8
Period: Week 8				
MEAN	33	38	59	25
SD	4.3	7.8	68.5	4.5
N	8	8	8	8
Period: Week 13				
MEAN	32	39	38	27
SD	6.0	9.4	12.1	6.8
N	8	8	8	8
Period: Week 18				
MEAN	35	40	29	25
SD	7.7	6.2	5.3	2.4
N	4	4	4	4
Period: Week 26				
MEAN	31	34	30	27
SD	5.4	8.5	12.8	4.6
N	4	4	4	4

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Aspartate Aminotransferase

STUDY ID: 097
STUDY NO: 097
ABBR: AST

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	32	31	33	34
SD	6.7	4.3	6.8	5.9
N	8	8	8	8
Period: Week -1				
MEAN	37	37	41	38
SD	8.0	5.5	12.6	6.0
N	8	8	8	8
Period: Week 2				
MEAN	39	43	48	47
SD	9.4	8.8	9.5	3.9
N	8	8	8	8
Period: Week 4				
MEAN	43	39	45	47
SD	13.1	7.3	9.5	4.0
N	8	8	8	8
Period: Week 8				
MEAN	39	44	54*	55*
SD	4.2	9.1	5.8	4.3
N	8	8	8	8
Period: Week 13				
MEAN	43	43	53	55*
SD	9.6	9.6	7.6	6.6
N	8	8	8	8
Period: Week 18				
MEAN	43	49	43	50
SD	6.0	7.2	7.9	10.4
N	4	4	4	4
Period: Week 26				
MEAN	41	40	39	40
SD	2.2	8.8	9.5	9.8
N	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.4

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Aspartate Aminotransferase

STUDY ID: 097
STUDY NO: 097
ABBR: AST

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	34	33	33	29	
SD	5.7	4.1	3.3	5.2	
N	8	8	8	8	
Period: Week -1					
MEAN	33	38	40	37	
SD	4.9	8.4	8.8	4.7	
N	8	8	8	8	
Period: Week 2					
MEAN	43	42	45	45	
SD	7.2	6.7	10.1	12.6	
N	8	8	8	8	
Period: Week 4					
MEAN	41	45	57*	42	
SD	5.5	6.8	17.9	7.9	
N	8	8	8	8	
Period: Week 8					
MEAN	44	43	58	50	
SD	5.7	5.1	17.4	13.1	
N	8	8	8	8	
Period: Week 13					
MEAN	41	44	56	59*	
SD	6.0	10.4	7.0	24.9	
N	8	8	8	8	
Period: Week 18					
MEAN	42	43	45	32	
SD	2.8	8.4	8.6	7.4	
N	4	4	4	4	
Period: Week 26					
MEAN	36	35	38	28	
SD	5.2	5.6	16.1	3.3	
N	4	4	4	4	

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Protein

STUDY ID: 097
STUDY NO: 097
ABBR: TP

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	6.4	6.2	6.3	6.3	
SD	0.19	0.41	0.42	0.43	
N	8	8	8	8	
Period: Week -1					
MEAN	6.5	6.5	6.3	6.5	
SD	0.30	0.35	0.38	0.27	
N	8	8	8	8	
Period: Week 2					
MEAN	6.7	6.7	7.0	7.0	
SD	0.44	0.32	0.32	0.16	
N	8	8	8	8	
Period: Week 4					
MEAN	6.7	6.5	6.5	6.6	
SD	0.31	0.36	0.27	0.18	
N	8	8	8	8	
Period: Week 8					
MEAN	6.4	6.4	6.4	6.5	
SD	0.37	0.27	0.33	0.31	
N	8	8	8	8	
Period: Week 13					
MEAN	6.4	6.3	6.4	6.4	
SD	0.34	0.20	0.37	0.52	
N	8	8	8	8	
Period: Week 18					
MEAN	6.4	6.4	6.4	6.6	
SD	0.47	0.26	0.53	0.41	
N	4	4	4	4	
Period: Week 26					
MEAN	6.8	6.5	6.6	6.7	
SD	0.22	0.27	0.49	0.26	
N	4	4	4	4	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Protein

STUDY IO: 097
STUDY NO: 097
ABBR: TP

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWEO BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	6.7	6.7	6.5	6.6
SD	0.44	0.27	0.47	0.18
N	8	8	8	8
Period: Week -1				
MEAN	6.5	6.2	6.5	6.2
SD	0.13	0.38	0.33	0.35
N	8	8	8	8
Period: Week 2				
MEAN	6.8	6.5	6.8	6.6
SO	0.32	0.26	0.38	0.44
N	8	8	8	8
Period: Week 4				
MEAN	6.3	6.5	6.5	6.2
SD	0.31	0.32	0.37	0.22
N	8	8	8	8
Period: Week 8				
MEAN	6.4	6.3	6.4	6.3
SD	0.43	0.35	0.24	0.46
N	8	8	8	8
Period: Week 13				
MEAN	6.6	6.5	6.7	6.2
SD	0.31	0.34	0.30	0.35
N	8	8	8	8
Period: Week 18				
MEAN	6.6	6.3	6.2	5.9
SD	0.38	0.29	0.31	0.33
N	4	4	4	4
Period: Week 26				
MEAN	6.3	6.2	6.5	6.4
SD	0.22	0.26	0.64	0.60
N	4	4	4	4

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Albumin

STUDY ID: 097
STUDY NO: 097
ABBR: ALB

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	3.2	3.2	3.1	3.2
SD	0.11	0.18	0.28	0.16
N	8	8	8	8
Period: Week -1				
MEAN	3.2	3.1	3.1	3.1
SD	0.24	0.19	0.16	0.21
N	8	8	8	8
Period: Week 2				
MEAN	3.2	3.2	3.3	3.3
SD	0.12	0.18	0.12	0.10
N	8	8	8	8
Period: Week 4				
MEAN	3.3	3.3	3.1	2.9*
SD	0.11	0.27	0.07	0.12
N	8	8	8	8
Period: Week 8				
MEAN	3.3	3.1	3.1	3.0
SD	0.16	0.10	0.17	0.23
N	8	8	8	8
Period: Week 13				
MEAN	3.3	3.2	3.2	3.0
SD	0.18	0.17	0.17	0.32
N	8	8	8	8
Period: Week 18				
MEAN	3.2	3.2	3.4	3.2
SD	0.24	0.15	0.14	0.25
N	4	4	4	4
Period: Week 26				
MEAN	3.6	3.4	3.5	3.6
SD	0.10	0.25	0.13	0.08
N	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.8

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Albumin

STUDY ID: 097
STUDY NO: 097
ABBR: ALB

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	3.4	3.4	3.5	3.4
SD	0.16	0.14	0.23	0.15
N	8	8	8	8
Period: Week -1				
MEAN	3.1	3.0	3.2	3.0
SD	0.17	0.23	0.20	0.17
N	8	8	8	8
Period: Week 2				
MEAN	3.2	3.1	3.4	3.1
SD	0.14	0.17	0.19	0.17
N	8	8	8	8
Period: Week 4				
MEAN	3.2	3.2	3.2	2.7*
SD	0.18	0.18	0.23	0.32
N	8	8	8	8
Period: Week 8				
MEAN	3.3	3.2	3.2	2.9*
SD	0.16	0.17	0.16	0.16
N	8	8	8	8
Period: Week 13				
MEAN	3.5	3.3	3.3	3.0*
SD	0.18	0.22	0.28	0.28
N	8	8	8	8
Period: Week 18				
MEAN	3.4	3.4	3.3	3.1
SD	0.17	0.14	0.38	0.14
N	4	4	4	4
Period: Week 26				
MEAN	3.5	3.3	3.7	3.5
SD	0.18	0.30	0.32	0.30
N	4	4	4	4

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Globulin

STUDY ID: 097
STUDY NO: 097
ABBR: GLOB

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	3.2	3.1	3.2	3.1	
SD	0.16	0.25	0.36	0.31	
N	8	8	8	8	
Period: Week -1					
MEAN	3.3	3.5	3.3	3.4	
SD	0.14	0.38	0.29	0.19	
N	8	8	8	8	
Period: Week 2					
MEAN	3.5	3.5	3.7	3.7	
SD	0.35	0.24	0.27	0.12	
N	8	8	8	8	
Period: Week 4					
MEAN	3.4	3.2	3.4	3.7	
SD	0.32	0.30	0.24	0.23	
N	8	8	8	8	
Period: Week 8					
MEAN	3.2	3.3	3.3	3.4	
SD	0.39	0.24	0.29	0.24	
N	8	8	8	8	
Period: Week 13					
MEAN	3.1	3.2	3.3	3.4	
SD	0.26	0.22	0.30	0.33	
N	8	8	8	8	
Period: Week 18					
MEAN	3.2	3.2	3.0	3.5	
SD	0.32	0.21	0.51	0.17	
N	4	4	4	4	
Period: Week 26					
MEAN	3.2	3.2	3.1	3.1	
SD	0.28	0.24	0.37	0.29	
N	4	4	4	4	

Table 7.10

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Globulin

STUDY ID: 097
STUDY NO: 097
ABBR: GLOB

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	3.3	3.2	3.0	3.3	
SD	0.36	0.22	0.26	0.13	
N	8	8	8	8	
Period: Week -1					
MEAN	3.4	3.2	3.3	3.2	
SD	0.17	0.22	0.29	0.31	
N	8	8	8	8	
Period: Week 2					
MEAN	3.6	3.4	3.5	3.5	
SD	0.24	0.21	0.29	0.33	
N	8	8	8	8	
Period: Week 4					
MEAN	3.1	3.4	3.3	3.5	
SD	0.27	0.31	0.31	0.33	
N	8	8	8	8	
Period: Week 8					
MEAN	3.1	3.1	3.3	3.4	
SD	0.40	0.34	0.23	0.52	
N	8	8	8	8	
Period: Week 13					
MEAN	3.2	3.2	3.3	3.3	
SD	0.21	0.18	0.29	0.37	
N	8	8	8	8	
Period: Week 18					
MEAN	3.2	2.9	3.0	2.8	
SD	0.24	0.40	0.10	0.29	
N	4	4	4	4	
Period: Week 26					
MEAN	2.8	2.9	2.8	2.9	
SD	0.05	0.38	0.37	0.34	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: A/G Ratio

STUDY ID: 097
STUDY NO: 097
ABBR: A/G

SEX: MALE

UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	1.01	1.03	0.99	1.03
SD	0.060	0.064	0.148	0.087
N	8	8	8	8
Period: Week -1				
MEAN	0.96	0.89	0.96	0.93
SD	0.076	0.122	0.072	0.090
N	8	8	8	8
Period: Week 2				
MEAN	0.91	0.90	0.90	0.90
SD	0.088	0.072	0.067	0.039
N	8	8	8	8
Period: Week 4				
MEAN	0.97	1.03	0.92	0.80*
SD	0.111	0.144	0.068	0.079
N	8	8	8	8
Period: Week 8				
MEAN	1.03	0.96	0.95	0.89
SD	0.142	0.084	0.106	0.102
N	8	8	8	8
Period: Week 13				
MEAN	1.06	1.01	0.98	0.91*
SD	0.098	0.101	0.088	0.117
N	8	8	8	8
Period: Week 18				
MEAN	0.99	1.00	1.18	0.91
SD	0.091	0.078	0.216	0.039
N	4	4	4	4
Period: Week 26				
MEAN	1.12	1.07	1.17	1.17
SD	0.118	0.129	0.105	0.130
N	4	4	4	4

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: A/G Ratio

STUDY ID: 097
STUDY NO: 097
ABBR: A/G

SEX: FEMALE

UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	1.04	1.07	1.15*	1.04	
SD	0.105	0.086	0.054	0.067	
N	8	8	8	8	
Period: Week -1					
MEAN	0.92	0.95	0.99	0.96	
SD	0.084	0.074	0.113	0.111	
N	8	8	8	8	
Period: Week 2					
MEAN	0.89	0.92	0.97	0.89	
SD	0.057	0.077	0.086	0.073	
N	8	8	8	8	
Period: Week 4					
MEAN	1.02	0.95	0.98	0.79*	
SD	0.113	0.110	0.127	0.157	
N	8	8	8	8	
Period: Week 8					
MEAN	1.05	1.04	0.97	0.85*	
SD	0.150	0.146	0.092	0.146	
N	8	8	8	8	
Period: Week 13					
MEAN	1.10	1.04	1.02	0.92*	
SD	0.074	0.065	0.152	0.150	
N	8	8	8	8	
Period: Week 18					
MEAN	1.09	1.21	1.11	1.13	
SD	0.061	0.216	0.162	0.120	
N	4	4	4	4	
Period: Week 26					
MEAN	1.24	1.16	1.34	1.22	
SD	0.054	0.252	0.133	0.091	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Bilirubin

STUDY ID: 097
STUDY NO: 097
ABBR: TBILI

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.12	0.11	0.12	0.11	
SD	0.034	0.020	0.020	0.023	
N	8	8	8	8	
Period: Week -1					
MEAN	0.13	0.10	0.12	0.10	
SD	0.024	0.042	0.020	0.056	
N	8	8	8	8	
Period: Week 2					
MEAN	0.18	0.19	0.22	0.27*	
SD	0.052	0.045	0.056	0.087	
N	8	8	8	8	
Period: Week 4					
MEAN	0.21	0.16	0.22	0.23	
SD	0.066	0.049	0.036	0.083	
N	8	8	8	8	
Period: Week 8					
MEAN	0.15	0.15	0.16	0.16	
SD	0.043	0.022	0.032	0.048	
N	8	8	8	8	
Period: Week 13					
MEAN	0.13	0.14	0.15	0.15	
SD	0.031	0.026	0.026	0.044	
N	8	8	8	8	
Period: Week 18					
MEAN	0.16	0.14	0.13	0.17	
SD	0.050	0.033	0.029	0.042	
N	4	4	4	4	
Period: Week 26					
MEAN	0.19	0.16	0.18	0.17	
SD	0.050	0.039	0.063	0.076	
N	4	4	4	4	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Bilirubin

STUDY ID: 097
STUDY NO: 097
ABBR: TBILI

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.09	0.09	0.10	0.09	
SD	0.014	0.013	0.012	0.026	
N	8	8	8	8	
Period: Week -1					
MEAN	0.11	0.10	0.13	0.10	
SD	0.024	0.031	0.024	0.038	
N	8	8	8	8	
Period: Week 2					
MEAN	0.22	0.17	0.27	0.26	
SD	0.116	0.050	0.073	0.076	
N	8	8	8	8	
Period: Week 4					
MEAN	0.19	0.19	0.25	0.18	
SD	0.058	0.038	0.051	0.054	
N	8	8	8	8	
Period: Week 8					
MEAN	0.17	0.16	0.19	0.14	
SD	0.042	0.042	0.050	0.025	
N	8	8	8	8	
Period: Week 13					
MEAN	0.17	0.18	0.18	0.13	
SD	0.031	0.059	0.029	0.044	
N	8	8	8	8	
Period: Week 18					
MEAN	0.22	0.17	0.16	0.12	
SD	0.066	0.044	0.029	0.026	
N	4	4	4	4	
Period: Week 26					
MEAN	0.15	0.17	0.18	0.14	
SD	0.046	0.037	0.049	0.010	
N	4	4	4	4	

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alkaline Phosphatase

STUDY ID: 097
STUDY NO: 097
ABBR: ALKP

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	132	158	121	120
SD	27.9	71.6	21.0	24.3
N	8	8	8	8
Period: Week -1				
MEAN	130	157	122	117
SD	19.7	55.6	30.1	23.4
N	8	8	8	8
Period: Week 2				
MEAN	139	154	113	110
SD	26.4	57.8	20.9	20.0
N	8	8	8	8
Period: Week 4				
MEAN	129	140	110	106
SD	26.8	51.2	24.5	22.9
N	8	8	8	8
Period: Week 8				
MEAN	115	125	104	98
SD	26.7	52.8	17.0	17.2
N	8	8	8	8
Period: Week 13				
MEAN	94	105	90	83
SD	19.3	38.8	23.2	13.3
N	8	8	8	8
Period: Week 18				
MEAN	91	92	92	96
SD	12.3	17.8	9.9	19.8
N	4	4	4	4
Period: Week 26				
MEAN	74	90	77	85
SD	5.3	30.2	21.0	20.5
N	4	4	4	4

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alkaline Phosphatase

STUDY ID: 097
STUDY NO: 097
ABBR: ALKP

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	114	139	121	136	
SD	12.1	34.1	56.2	45.0	
N	8	8	8	8	
Period: Week -1					
MEAN	114	141	123	127	
SD	16.7	53.1	61.1	44.6	
N	8	8	8	8	
Period: Week 2					
MEAN	120	153	125	135	
SD	17.8	44.6	59.3	64.4	
N	8	8	8	8	
Period: Week 4					
MEAN	111	125	117	117	
SD	15.7	31.6	40.7	21.3	
N	8	8	8	8	
Period: Week 8					
MEAN	98	118	110	96	
SD	21.1	23.4	47.8	16.9	
N	8	8	8	8	
Period: Week 13					
MEAN	95	105	101	106	
SD	31.0	21.3	37.1	28.6	
N	8	8	8	8	
Period: Week 18					
MEAN	79	94	94	108	
SD	15.2	29.5	40.1	36.0	
N	4	4	4	4	
Period: Week 26					
MEAN	71	99	97	116	
SD	15.6	39.6	35.2	31.7	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Gamma Glutamyl Transferase

STUDY ID: 097
STUDY NO: 097
ABBR: GGT

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	3	3	4	3
SD	1.4	1.8	1.1	1.6
N	8	8	8	8
Period: Week -1				
MEAN	2	1	2	2
SD	2.2	1.0	1.3	1.7
N	8	8	8	8
Period: Week 2				
MEAN	1	1	1	1
SD	0.7	1.5	1.2	1.2
N	8	8	8	8
Period: Week 4				
MEAN	3	2	2	2
SD	1.3	0.7	1.2	1.2
N	8	8	8	8
Period: Week 8				
MEAN	3	4	3	2
SD	1.5	1.8	1.3	1.4
N	8	8	8	8
Period: Week 13				
MEAN	2	2	1	2
SD	1.6	1.0	1.5	1.6
N	8	8	8	8
Period: Week 18				
MEAN	2	4	4	3
SD	1.5	0.6	2.6	1.3
N	4	4	4	4
Period: Week 26				
MEAN	3	3	5	5
SD	1.0	1.4	0.6	0.6
N	4	4	4	4

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Gamma Glutamyl Transferase

STUDY ID: 097
STUDY NO: 097
ABBR: GGT

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	4	3	3	3	
SD	1.4	1.5	1.4	0.8	
N	8	8	8	8	
Period: Week -1					
MEAN	2	2	3	1	
SD	2.1	1.3	1.8	0.9	
N	8	8	8	8	
Period: Week 2					
MEAN	1	1	1	1	
SD	0.9	1.2	0.7	1.1	
N	8	8	8	8	
Period: Week 4					
MEAN	1	2	2	2	
SD	1.3	0.9	1.5	1.6	
N	8	8	8	8	
Period: Week 8					
MEAN	3	4	3	3	
SD	1.9	1.4	1.9	1.8	
N	8	8	8	8	
Period: Week 13					
MEAN	1	2	2	2	
SD	1.7	1.5	1.8	1.3	
N	8	8	8	8	
Period: Week 18					
MEAN	4	4	3	3	
SD	1.3	1.9	1.5	1.6	
N	4	4	4	4	
Period: Week 26					
MEAN	4	3	6	3	
SD	2.7	1.7	1.3	1.7	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Cholesterol

STUDY ID: 097
STUDY NO: 097
ABBR: CHOL

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	199	198	190	199	
SD	33.7	34.9	20.9	30.4	
N	8	8	8	8	
Period: Week -1					
MEAN	188	193	170	183	
SD	23.8	33.6	23.1	24.4	
N	8	8	8	8	
Period: Week 2					
MEAN	179	187	177	178	
SD	34.6	42.4	30.4	19.3	
N	8	8	8	8	
Period: Week 4					
MEAN	199	189	172	186	
SD	30.8	35.6	14.3	16.9	
N	8	8	8	8	
Period: Week 8					
MEAN	149	163	146	157	
SD	12.7	27.7	20.0	14.4	
N	8	8	8	8	
Period: Week 13					
MEAN	147	158	142	146	
SD	24.4	29.5	12.1	25.4	
N	8	8	8	8	
Period: Week 18					
MEAN	151	175	151	163	
SD	5.3	35.1	27.7	36.2	
N	4	4	4	4	
Period: Week 26					
MEAN	162	198*	173	169	
SD	11.0	23.7	15.7	3.9	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Cholesterol

STUDY ID: 097
STUDY NO: 097
ABBR: CHOL

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	196	191	187	194	
SD	29.3	29.9	24.7	26.7	
N	8	8	8	8	
Period: Week -1					
MEAN	187	183	190	183	
SD	21.3	27.1	28.5	27.0	
N	8	8	8	8	
Period: Week 2					
MEAN	179	177	174	182	
SD	21.5	31.4	32.3	47.3	
N	8	8	8	8	
Period: Week 4					
MEAN	186	204	188	186	
SD	18.9	38.0	40.9	35.2	
N	8	8	8	8	
Period: Week 8					
MEAN	165	192	164	155	
SD	19.8	48.5	25.7	30.6	
N	8	8	8	8	
Period: Week 13					
MEAN	191	182	179	165	
SD	39.7	31.8	49.5	28.9	
N	8	8	8	8	
Period: Week 18					
MEAN	213	185	195	164	
SD	38.2	26.9	25.9	46.7	
N	4	4	4	4	
Period: Week 26					
MEAN	206	219	225	196	
SD	37.5	73.2	55.5	59.6	
N	4	4	4	4	

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Triglycerides

STUDY ID: 097
STUDY NO: 097
ABBR: TRY

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	42	44	45	44
SD	13.4	8.0	8.4	8.1
N	8	8	8	8
Period: Week -1				
MEAN	46	45	45	50
SD	9.4	12.5	17.5	12.8
N	8	8	8	8
Period: Week 2				
MEAN	33	38	34	37
SD	11.8	17.5	13.3	8.2
N	8	8	8	8
Period: Week 4				
MEAN	46	44	47	53
SD	10.3	11.6	11.5	11.2
N	8	8	8	8
Period: Week 8				
MEAN	34	29	34	56*
SD	10.7	7.1	9.9	16.9
N	8	8	8	8
Period: Week 13				
MEAN	37	44	38	47
SD	13.4	9.4	12.7	18.9
N	8	8	8	8
Period: Week 18				
MEAN	41	34	31	45
SD	16.4	8.2	1.2	9.9
N	4	4	4	4
Period: Week 26				
MEAN	37	42	44	50
SD	8.7	10.5	19.4	16.4
N	4	4	4	4

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Triglycerides

STUDY ID: 097
STUDY NO: 097
ABBR: TRY

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	43	43	35	38	
SD	12.3	10.9	6.1	6.1	
N	8	8	8	8	
Period: Week -1					
MEAN	41	44	44	39	
SD	9.0	13.0	10.2	12.4	
N	8	8	8	8	
Period: Week 2					
MEAN	35	38	39	34	
SD	16.0	5.4	13.9	10.1	
N	8	8	8	8	
Period: Week 4					
MEAN	44	50	54	52	
SD	10.3	5.8	15.9	11.1	
N	8	8	8	8	
Period: Week 8					
MEAN	34	41	45	42	
SD	13.9	8.6	19.0	11.1	
N	8	8	8	8	
Period: Week 13					
MEAN	41	40	46	51	
SD	15.8	16.9	21.2	12.6	
N	8	8	8	8	
Period: Week 18					
MEAN	44	34	39	38	
SD	9.9	7.4	14.9	9.4	
N	4	4	4	4	
Period: Week 26					
MEAN	41	41	37	33	
SD	11.4	15.6	7.8	5.7	
N	4	4	4	4	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Lactate Dehydrogenase

STUDY ID: 097
STUDY NO: 097
ABBR: LDH

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	104	53	76	73
SD	73.7	9.7	48.3	48.2
N	8	8	8	8
Period: Week -1				
MEAN	116	126	163	125
SD	84.1	79.9	164.8	97.2
N	8	8	8	8
Period: Week 2				
MEAN	86	75	102	78
SD	81.0	44.7	82.8	52.7
N	8	8	8	8
Period: Week 4				
MEAN	60	77	111	116
SD	20.0	31.4	94.6	91.3
N	8	8	8	8
Period: Week 8				
MEAN	39	58	76	78
SD	7.5	40.7	45.9	29.6
N	8	8	8	8
Period: Week 13				
MEAN	87	100	119	71
SD	96.1	100.1	69.9	28.5
N	8	8	8	8
Period: Week 18				
MEAN	108	98	63	47
SD	129.1	81.1	41.0	23.7
N	4	4	4	4
Period: Week 26				
MEAN	139	73	38	93
SD	109.8	46.3	10.4	108.4
N	4	4	4	4

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Lactate Dehydrogenase

STUDY ID: 097
STUDY NO: 097
ABBR: LDH

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	90	120	87	86	
SD	37.3	61.1	36.0	62.5	
N	8	8	8	8	
Period: Week -1					
MEAN	57	131	71	90	
SD	25.9	140.4	40.1	53.8	
N	8	8	8	8	
Period: Week 2					
MEAN	83	61	75	82	
SD	61.9	25.9	60.1	49.3	
N	8	8	8	8	
Period: Week 4					
MEAN	61	110	120	119	
SD	30.4	114.4	66.4	95.1	
N	8	8	8	8	
Period: Week 8					
MEAN	53	58	90	77	
SD	13.0	24.7	62.7	39.0	
N	8	8	8	8	
Period: Week 13					
MEAN	78	70	68	103	
SD	53.2	47.1	28.2	79.4	
N	8	8	8	8	
Period: Week 18					
MEAN	104	69	63	51	
SD	63.9	45.1	16.1	30.3	
N	4	4	4	4	
Period: Week 26					
MEAN	57	43	64	52	
SD	48.9	10.2	30.0	11.8	
N	4	4	4	4	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatine Kinase

STUDY ID: 097
STUDY NO: 097
ABBR: CK

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	283	194	261	252
SD	119.9	39.3	89.5	114.6
N	8	8	8	8
Period: Week -1				
MEAN	255	230	297	276
SD	76.3	95.7	141.5	111.7
N	8	8	8	8
Period: Week 2				
MEAN	287	282	294	254
SD	162.9	181.0	185.8	50.0
N	8	8	8	8
Period: Week 4				
MEAN	307	251	235	259
SD	197.2	106.1	115.7	115.6
N	8	8	8	8
Period: Week 8				
MEAN	225	200	247	227
SD	60.9	115.4	84.1	77.7
N	8	8	8	8
Period: Week 13				
MEAN	221	215	289	214
SD	72.5	99.1	103.9	87.5
N	8	8	8	8
Period: Week 18				
MEAN	226	209	232	257
SD	103.1	55.9	143.0	90.7
N	4	4	4	4
Period: Week 26				
MEAN	248	138	194	234
SD	78.2	47.2	102.4	72.2
N	4	4	4	4

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatine Kinase

STUDY ID: 097
STUDY NO: 097
ABBR: CK

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	200	206	190	177	
SD	52.4	40.3	45.3	44.1	
N	8	8	8	8	
Period: Week -1					
MEAN	153	215	236	211	
SD	48.3	95.7	123.9	71.5	
N	8	8	8	8	
Period: Week 2					
MEAN	244	275	209	179	
SD	88.4	134.7	48.8	66.0	
N	8	8	8	8	
Period: Week 4					
MEAN	213	307	355	157	
SD	61.5	217.8	312.8	62.1	
N	8	8	8	8	
Period: Week 8					
MEAN	284	262	227	161	
SD	104.0	107.6	119.1	51.2	
N	8	8	8	8	
Period: Week 13					
MEAN	207	218	214	172	
SD	52.2	93.8	72.9	63.6	
N	8	8	8	8	
Period: Week 18					
MEAN	183	184	226	146	
SD	35.6	52.1	42.2	31.3	
N	4	4	4	4	
Period: Week 26					
MEAN	156	165	190	119	
SD	30.6	44.4	126.5	29.6	
N	4	4	4	4	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Blood Urea Nitrogen

STUDY ID: 097
STUDY NO: 097
ABBR: BUN

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	11.8	11.4	11.5	12.1	
SD	1.15	1.76	2.12	1.72	
N	8	8	8	8	
Period: Week -1					
MEAN	12.5	11.0	11.2	12.8	
SD	2.49	1.23	1.76	1.38	
N	8	8	8	8	
Period: Week 2					
MEAN	14.1	13.8	13.5	14.1	
SD	1.27	2.41	2.37	2.05	
N	8	8	8	8	
Period: Week 4					
MEAN	14.1	14.1	14.0	16.2	
SD	2.13	2.83	2.44	2.97	
N	8	8	8	8	
Period: Week 8					
MEAN	15.0	14.5	14.2	15.7	
SD	2.47	2.04	1.25	3.46	
N	8	8	8	8	
Period: Week 13					
MEAN	14.7	14.5	14.7	16.2	
SD	2.39	1.86	1.06	3.08	
N	8	8	8	8	
Period: Week 18					
MEAN	14.8	13.5	13.2	16.2	
SD	0.70	1.98	1.19	2.18	
N	4	4	4	4	
Period: Week 26					
MEAN	14.7	14.3	14.0	16.1	
SD	1.92	3.64	3.23	2.92	
N	4	4	4	4	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Blood Urea Nitrogen

STUDY ID: 097
STUDY NO: 097
ABBR: BUN

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	12.0	11.5	11.8	11.0	
SD	1.82	1.76	1.68	0.86	
N	8	8	8	8	
Period: Week -1					
MEAN	12.6	11.3	12.9	12.6	
SD	1.85	2.42	1.49	1.90	
N	8	8	8	8	
Period: Week 2					
MEAN	15.1	14.0	13.8	14.4	
SD	2.50	1.75	1.68	2.00	
N	8	8	8	8	
Period: Week 4					
MEAN	14.6	14.1	14.2	12.3	
SD	1.32	1.57	2.38	1.52	
N	8	8	8	8	
Period: Week 8					
MEAN	14.9	16.3	15.2	15.0	
SD	2.32	1.34	3.19	1.84	
N	8	8	8	8	
Period: Week 13					
MEAN	14.9	15.3	16.4	14.0	
SD	2.37	2.03	2.38	1.24	
N	8	8	8	8	
Period: Week 18					
MEAN	15.6	15.5	15.2	16.5	
SD	1.32	2.29	1.12	1.70	
N	4	4	4	4	
Period: Week 26					
MEAN	13.9	16.3	14.5	15.1	
SD	1.38	1.69	2.61	1.21	
N	4	4	4	4	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatinine

STUDY ID: 097
STUDY NO: 097
ABBR: CREA

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	0.62	0.61	0.62	0.66
SD	0.044	0.056	0.034	0.059
N	8	8	8	8
Period: Week -1				
MEAN	0.69	0.68	0.68	0.69
SD	0.061	0.064	0.036	0.067
N	8	8	8	8
Period: Week 2				
MEAN	0.70	0.67	0.72	0.77
SD	0.036	0.077	0.029	0.072
N	8	8	8	8
Period: Week 4				
MEAN	0.70	0.71	0.72	0.72
SD	0.049	0.075	0.078	0.066
N	8	8	8	8
Period: Week 8				
MEAN	0.72	0.73	0.77	0.79
SD	0.050	0.078	0.060	0.095
N	8	8	8	8
Period: Week 13				
MEAN	0.70	0.73	0.75	0.72
SD	0.043	0.057	0.050	0.047
N	8	8	8	8
Period: Week 18				
MEAN	0.73	0.74	0.76	0.76
SD	0.017	0.047	0.070	0.084
N	4	4	4	4
Period: Week 26				
MEAN	0.78	0.76	0.77	0.82
SD	0.029	0.088	0.049	0.083
N	4	4	4	4

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatinine

STUDY ID: 097
STUDY NO: 097
ABBR: CREA

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.68	0.68	0.66	0.65	
SD	0.048	0.055	0.047	0.036	
N	8	8	8	8	
Period: Week -1					
MEAN	0.71	0.70	0.71	0.67	
SD	0.053	0.088	0.033	0.048	
N	8	8	8	8	
Period: Week 2					
MEAN	0.70	0.71	0.76	0.69	
SD	0.054	0.072	0.054	0.060	
N	8	8	8	8	
Period: Week 4					
MEAN	0.71	0.73	0.74	0.67	
SD	0.050	0.055	0.037	0.032	
N	8	8	8	8	
Period: Week 8					
MEAN	0.72	0.75	0.77	0.75	
SD	0.068	0.084	0.055	0.059	
N	8	8	8	8	
Period: Week 13					
MEAN	0.69	0.72	0.74	0.68	
SD	0.046	0.076	0.083	0.096	
N	8	8	8	8	
Period: Week 18					
MEAN	0.81	0.77	0.74	0.67	
SD	0.057	0.037	0.102	0.089	
N	4	4	4	4	
Period: Week 26					
MEAN	0.73	0.74	0.75	0.68	
SD	0.067	0.024	0.040	0.021	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sodium

STUDY ID: 097
STUDY NO: 097
ABBR: NA

SEX: MALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	143	144	144	143
SD	1.8	1.2	1.0	0.9
N	8	8	8	8
Period: Week -1				
MEAN	143	145	144	143
SD	1.9	1.1	1.2	1.0
N	8	8	8	8
Period: Week 2				
MEAN	144	144	145	145
SD	1.2	0.7	1.5	0.9
N	8	8	8	8
Period: Week 4				
MEAN	146	145	146	145
SD	1.3	1.3	1.4	1.3
N	8	8	8	8
Period: Week 8				
MEAN	145	144	145	144
SD	1.6	1.5	1.7	1.2
N	8	8	8	8
Period: Week 13				
MEAN	145	145	145	144
SD	1.6	1.4	0.8	1.5
N	8	8	8	8
Period: Week 18				
MEAN	145	145	146	145
SD	0.8	1.3	1.3	1.8
N	4	4	4	4
Period: Week 26				
MEAN	146	143	145	144
SD	1.0	1.0	1.3	1.5
N	4	4	4	4

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sodium

STUDY ID: 097
STUDY NO: 097
ABBR: NA

SEX: FEMALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	145	143	144	143	
SD	1.3	1.0	1.6	0.9	
N	8	8	8	8	
Period: Week -1					
MEAN	144	144	144	143	
SD	1.9	0.5	0.8	1.0	
N	8	8	8	8	
Period: Week 2					
MEAN	143	144	144	144	
SD	1.5	1.3	1.1	1.3	
N	8	8	8	8	
Period: Week 4					
MEAN	145	145	145	144	
SD	1.2	0.9	1.5	2.1	
N	8	8	8	8	
Period: Week 8					
MEAN	145	143	144	144	
SD	1.1	1.4	1.7	2.4	
N	8	8	8	8	
Period: Week 13					
MEAN	144	145	144	144	
SD	2.0	1.2	1.5	2.4	
N	8	8	8	8	
Period: Week 18					
MEAN	145	145	144	143	
SD	1.7	1.7	1.5	0.5	
N	4	4	4	4	
Period: Week 26					
MEAN	145	142*	143*	145	
SD	1.0	0.8	0.5	2.2	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Potassium

STUDY ID: 097
STUDY NO: 097
ABBR: K

SEX: MALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	4.61	4.84	4.93*	4.63	
SD	0.195	0.222	0.191	0.168	
N	8	8	8	8	
Period: Week -1					
MEAN	4.61	4.65	4.44	4.48	
SD	0.217	0.220	0.313	0.205	
N	8	8	8	8	
Period: Week 2					
MEAN	4.45	4.30	4.29	4.29	
SD	0.328	0.244	0.304	0.245	
N	8	8	8	8	
Period: Week 4					
MEAN	4.36	4.46	4.40	4.31	
SD	0.241	0.235	0.196	0.209	
N	8	8	8	8	
Period: Week 8					
MEAN	4.43	4.43	4.45	4.32	
SD	0.355	0.226	0.224	0.214	
N	8	8	8	8	
Period: Week 13					
MEAN	4.30	4.51	4.30	4.45	
SD	0.275	0.346	0.245	0.264	
N	8	8	8	8	
Period: Week 18					
MEAN	4.52	4.52	4.55	4.32	
SD	0.293	0.274	0.113	0.242	
N	4	4	4	4	
Period: Week 26					
MEAN	4.27	4.47	4.28	4.32	
SD	0.094	0.303	0.173	0.300	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Potassium

STUDY ID: 097
STUDY NO: 097
ABBR: K

SEX: FEMALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	4.54	4.61	4.68	4.83	
SD	0.375	0.219	0.227	0.242	
N	8	8	8	8	
Period: Week -1					
MEAN	4.32	4.45	4.51	4.38	
SD	0.228	0.168	0.194	0.145	
N	8	8	8	8	
Period: Week 2					
MEAN	4.23	4.17	4.22	4.23	
SD	0.210	0.155	0.182	0.232	
N	8	8	8	8	
Period: Week 4					
MEAN	4.39	4.44	4.31	4.49	
SD	0.269	0.307	0.202	0.268	
N	8	8	8	8	
Period: Week 8					
MEAN	4.37	4.19	4.44	4.48	
SD	0.292	0.203	0.313	0.170	
N	8	8	8	8	
Period: Week 13					
MEAN	4.30	4.33	4.42	4.48	
SD	0.150	0.205	0.312	0.163	
N	8	8	8	8	
Period: Week 18					
MEAN	4.61	4.27	4.43	4.38	
SD	0.287	0.128	0.129	0.374	
N	4	4	4	4	
Period: Week 26					
MEAN	4.26	4.16	4.36	4.58	
SD	0.323	0.419	0.491	0.334	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Chloride

STUDY ID: 097
STUDY NO: 097
ABBR: CL

SEX: MALE

UNITS: mEq/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg/base/kg/day
Period: Week -3					
MEAN	120	118	120	119	
SD	2.4	2.6	3.0	2.7	
N	8	8	8	8	
Period: Week -1					
MEAN	115	118	116	119	
SD	3.4	4.2	3.3	2.7	
N	8	8	8	8	
Period: Week 2					
MEAN	123	124	125	128	
SD	2.9	4.9	2.1	12.6	
N	8	8	8	8	
Period: Week 4					
MEAN	121	118*	120	121	
SD	2.1	2.9	1.7	1.6	
N	8	8	8	8	
Period: Week 8					
MEAN	128	127	122	123	
SD	14.3	8.7	4.8	1.4	
N	8	8	8	8	
Period: Week 13					
MEAN	119	116	122	120	
SD	3.8	3.3	6.7	3.9	
N	8	8	8	8	
Period: Week 18					
MEAN	117	118	116	116	
SD	2.5	2.2	2.8	3.1	
N	4	4	4	4	
Period: Week 26					
MEAN	124	123	126	123	
SD	1.0	1.7	5.3	2.8	
N	4	4	4	4	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Chloride

STUDY ID: 097
STUDY NO: 097
ABBR: CL

SEX: FEMALE

UNITS: mEq/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	122	123	120	121	
SD	3.6	2.6	3.1	2.9	
N	8	8	8	8	
Period: Week -1					
MEAN	117	114	116	116	
SD	2.0	2.7	4.6	3.3	
N	8	8	8	8	
Period: Week 2					
MEAN	128	123	136	131	
SD	12.0	2.8	32.8	18.9	
N	8	8	8	8	
Period: Week 4					
MEAN	119	121	119	118	
SD	2.7	3.3	3.2	4.5	
N	8	8	8	8	
Period: Week 8					
MEAN	125	122	123	123	
SD	6.9	3.2	4.8	4.1	
N	8	8	8	8	
Period: Week 13					
MEAN	119	120	121	118	
SD	5.0	4.4	5.3	6.0	
N	8	8	8	8	
Period: Week 18					
MEAN	116	116	118	117	
SD	3.6	1.0	3.0	1.9	
N	4	4	4	4	
Period: Week 26					
MEAN	123	122	120	122	
SD	2.6	1.6	3.6	3.2	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Calcium

STUDY ID: 097
STUDY NO: 097
ABBR: CA

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg/base/kg/day
Period: Week -3					
MEAN	10.3	10.2	10.1	10.1	
SD	0.38	0.32	0.25	0.29	
N	8	8	8	8	
Period: Week -1					
MEAN	10.4	10.3	10.3	10.3	
SD	0.45	0.22	0.31	0.18	
N	8	8	8	8	
Period: Week 2					
MEAN	10.5	10.2	10.4	10.5	
SD	0.25	0.30	0.26	0.20	
N	8	8	8	8	
Period: Week 4					
MEAN	10.2	10.0	9.9	10.1	
SD	0.38	0.33	0.39	0.31	
N	8	8	8	8	
Period: Week 8					
MEAN	10.0	9.7	9.7	9.9	
SD	0.33	0.30	0.33	0.31	
N	8	8	8	8	
Period: Week 13					
MEAN	10.0	9.8	10.1	9.9	
SD	0.31	0.64	0.46	0.45	
N	8	8	8	8	
Period: Week 18					
MEAN	10.2	10.0	10.1	10.3	
SD	0.51	0.17	0.19	0.33	
N	4	4	4	4	
Period: Week 26					
MEAN	10.1	9.9	9.9	10.1	
SD	0.22	0.60	0.44	0.34	
N	4	4	4	4	

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Calcium

STUDY ID: 097
STUDY NO: 097
ABBR: CA

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	10.3	10.5	10.4	10.4	
SD	0.33	0.40	0.43	0.35	
N	8	8	8	8	
Period: Week -1					
MEAN	10.2	10.4	10.5	10.2	
SD	0.34	0.38	0.24	0.12	
N	8	8	8	8	
Period: Week 2					
MEAN	10.3	10.3	10.5	10.2	
SD	0.24	0.29	0.24	0.39	
N	8	8	8	8	
Period: Week 4					
MEAN	10.0	10.3	10.0	9.7	
SD	0.26	0.41	0.26	0.29	
N	8	8	8	8	
Period: Week 8					
MEAN	9.9	10.0	9.8	9.7	
SD	0.32	0.57	0.37	0.21	
N	8	8	8	8	
Period: Week 13					
MEAN	10.2	10.2	10.1	9.7	
SD	0.35	0.32	0.52	0.50	
N	8	8	8	8	
Period: Week 18					
MEAN	10.3	10.1	10.2	10.2	
SD	0.38	0.08	0.50	0.24	
N	4	4	4	4	
Period: Week 26					
MEAN	10.4	9.9	10.2	10.1	
SD	0.56	0.28	0.24	0.47	
N	4	4	4	4	

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Inorganic Phosphorus

STUDY ID: 097
STUDY NO: 097
ABBR: IP

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	6.2	6.3	6.3	5.7
SD	0.78	0.69	0.62	0.61
N	8	8	8	8
Period: Week -1				
MEAN	5.7	5.6	5.6	5.5
SD	0.79	0.38	0.59	0.61
N	8	8	8	8
Period: Week 2				
MEAN	6.0	5.7	5.4	5.3*
SD	0.71	0.25	0.47	0.45
N	8	8	8	8
Period: Week 4				
MEAN	5.7	5.6	5.3	5.1
SD	0.63	0.67	0.60	0.39
N	8	8	8	8
Period: Week 8				
MEAN	5.4	4.9	5.0	4.8
SD	0.55	0.77	0.77	0.49
N	8	8	8	8
Period: Week 13				
MEAN	4.6	4.7	4.4	4.8
SD	0.71	0.50	0.82	0.38
N	8	8	8	8
Period: Week 18				
MEAN	4.9	4.6	4.8	4.9
SD	0.66	0.98	0.57	0.26
N	4	4	4	4
Period: Week 26				
MEAN	4.2	4.5	4.6	4.1
SD	0.93	0.63	1.03	1.06
N	4	4	4	4

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Inorganic Phosphorus

STUDY ID: 097
STUDY NO: 097
ABBR: IP

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	5.7	5.4	6.0	5.7	
SD	0.51	0.59	0.74	0.83	
N	8	8	8	8	
Period: Week -1					
MEAN	5.4	5.5	5.3	5.4	
SD	0.56	0.47	0.48	0.26	
N	8	8	8	8	
Period: Week 2					
MEAN	5.2	4.9	5.0	5.3	
SD	1.01	0.47	0.71	0.45	
N	8	8	8	8	
Period: Week 4					
MEAN	5.2	5.3	5.2	5.2	
SD	0.44	0.35	0.68	0.36	
N	8	8	8	8	
Period: Week 8					
MEAN	4.7	4.8	4.4	4.8	
SD	0.34	0.64	0.35	0.45	
N	8	8	8	8	
Period: Week 13					
MEAN	4.3	4.6	4.5	4.7	
SD	0.64	0.43	0.77	0.71	
N	8	8	8	8	
Period: Week 18					
MEAN	4.5	4.0*	3.8*	4.3	
SD	0.38	0.14	0.30	0.22	
N	4	4	4	4	
Period: Week 26					
MEAN	4.4	3.8	3.9	3.9	
SD	0.70	0.26	0.76	0.22	
N	4	4	4	4	

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Glucose

STUDY ID: 097
STUDY NO: 097
ABBR: GLU

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	125	115	118	119	
SD	7.5	15.4	11.6	10.2	
N	8	8	8	8	
Period: Week -1					
MEAN	118	119	117	120	
SD	5.2	17.7	7.3	10.6	
N	8	8	8	8	
Period: Week 2					
MEAN	122	126	122	126	
SD	11.4	15.1	12.0	14.8	
N	8	8	8	8	
Period: Week 4					
MEAN	116	114	115	115	
SD	10.6	9.7	4.8	6.7	
N	8	8	8	8	
Period: Week 8					
MEAN	121	121	117	112	
SD	7.9	11.1	6.9	13.5	
N	8	8	8	8	
Period: Week 13					
MEAN	116	113	111	108	
SD	11.3	11.3	6.6	8.4	
N	8	8	8	8	
Period: Week 18					
MEAN	123	119	115	120	
SD	7.5	4.5	9.3	11.9	
N	4	4	4	4	
Period: Week 26					
MEAN	122	116	114	108	
SD	11.8	7.3	2.8	19.6	
N	4	4	4	4	

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Glucose

STUDY ID: 097
STUDY NO: 097
ABBR: GLU

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	122	117	114	121	
SD	8.4	7.2	10.6	6.9	
N	8	8	8	8	
Period: Week -1					
MEAN	115	106	113	115	
SD	8.2	13.5	9.5	9.2	
N	8	8	8	8	
Period: Week 2					
MEAN	124	116	120	120	
SD	12.5	10.6	14.4	8.4	
N	8	8	8	8	
Period: Week 4					
MEAN	111	115	109	103	
SD	11.2	9.0	7.4	8.2	
N	8	8	8	8	
Period: Week 8					
MEAN	115	113	111	109	
SD	10.7	5.7	12.2	10.1	
N	8	8	8	8	
Period: Week 13					
MEAN	112	110	108	99	
SD	12.8	11.8	10.7	13.4	
N	8	8	8	8	
Period: Week 18					
MEAN	113	113	113	108	
SD	7.4	12.7	12.1	12.0	
N	4	4	4	4	
Period: Week 26					
MEAN	109	116	105	109	
SD	8.2	6.5	5.0	11.2	
N	4	4	4	4	

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Haptoglobin

STUDY ID: 097
STUDY NO: 097
ABBR: HAPT

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	70.1	71.9	70.2	81.0
SD	50.47	33.44	39.43	40.59
N	8	8	8	8
Period: Week -1				
MEAN	71.5	122.0	75.0	91.1
SD	35.87	36.40	41.36	46.49
N	7	8	8	8
Period: Week 2				
MEAN	79.5	97.0	114.5	98.3
SD	59.55	48.03	39.34	73.89
N	5	8	7	8
Period: Week 4				
MEAN	74.4	99.0	203.3*	246.9*
SD	52.54	32.64	50.69	90.91
N	5	8	8	8
Period: Week 8				
MEAN	87.5	88.9	150.5	178.6*
SD	52.80	64.62	42.94	65.92
N	5	8	8	8
Period: Week 13				
MEAN	76.1	85.5	94.3	138.3
SD	52.09	47.38	44.86	75.20
N	3	7	8	8
Period: Week 18				
MEAN	76.8	92.3	105.0	89.3
SD	47.25	57.67	21.03	52.99
N	4	4	3	4
Period: Week 26				
MEAN	152.6	287.0	65.6	65.9
SD	45.61	171.95	34.42	42.75
N	2	3	4	4

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Haptoglobin

STUDY ID: 097
STUDY NO: 097
ABBR: HAPT

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	58.2	59.0	68.2	85.6	
SD	36.18	27.53	26.73	33.60	
N	8	8	8	8	
Period: Week -1					
MEAN	79.5	93.0	62.4	73.0	
SD	75.49	54.73	30.49	35.73	
N	7	7	8	7	
Period: Week 2					
MEAN	60.9	58.3	44.7	98.3	
SD	40.09	30.67	31.31	52.65	
N	4	4	5	8	
Period: Week 4					
MEAN	30.3	38.6	122.8	324.2*	
SD	12.83	23.55	76.74	105.36	
N	3	3	8	8	
Period: Week 8					
MEAN	40.9	85.4	90.6	210.3*	
SD	31.02	NA	43.24	75.58	
N	3	1	5	7	
Period: Week 13					
MEAN	NA	206.4	63.6	152.7	
SD	NA	NA	26.05	47.05	
N	0	1	4	6	
Period: Week 18					
MEAN	29.9	NA	103.4	47.3	
SD	18.10	NA	NA	27.00	
N	2	0	1	4	
Period: Week 26					
MEAN	41.2	38.7	57.1	86.8	
SD	36.20	37.66	NA	30.36	
N	2	3	1	3	

*-Significant Difference from Control P < .05 NA-Not Applicable

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Erythrocytes

STUDY ID: 097
STUDY NO: 097
ABBR: RBC

SEX: MALE

UNITS: 10^6/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	6.14	6.35	6.56	6.43	
SD	0.438	0.309	0.429	0.541	
N	8	8	8	8	
Period: Week -1					
MEAN	6.31	6.29	6.33	6.53	
SD	0.636	0.268	0.597	0.352	
N	8	8	8	8	
Period: Week 2					
MEAN	6.12	6.25	6.42	6.24	
SD	0.590	0.474	0.505	0.447	
N	8	8	8	8	
Period: Week 4					
MEAN	6.27	6.31	5.72*	5.44*	
SD	0.398	0.257	0.506	0.429	
N	8	8	8	8	
Period: Week 8					
MEAN	6.19	6.46	6.32	6.35	
SD	0.198	0.483	0.571	0.433	
N	8	8	8	8	
Period: Week 13					
MEAN	6.34	6.64	6.28	6.11	
SD	0.450	0.679	0.618	0.795	
N	8	8	8	8	
Period: Week 18					
MEAN	6.91	6.63	7.60	6.72	
SD	0.462	0.209	0.805	0.658	
N	4	4	4	4	
Period: Week 26					
MEAN	7.25	6.98	7.54	7.46	
SD	0.261	0.598	0.499	0.312	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Erythrocytes

STUDY ID: 097
STUDY NO: 097
ABBR: RBC

SEX: FEMALE

UNITS: 10^6/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	6.40	6.54	6.49	6.35
SD	0.324	0.404	0.367	0.283
N	8	8	8	8
Period: Week -1				
MEAN	6.37	6.37	6.53	6.12
SD	0.391	0.305	0.443	0.508
N	8	8	8	8
Period: Week 2				
MEAN	6.38	6.36	6.36	5.84*
SD	0.309	0.333	0.411	0.328
N	8	8	8	8
Period: Week 4				
MEAN	6.31	6.39	5.79*	5.28*
SD	0.372	0.227	0.380	0.471
N	8	8	8	8
Period: Week 8				
MEAN	6.43	6.48	6.26	6.20
SD	0.413	0.435	0.484	0.328
N	8	8	8	8
Period: Week 13				
MEAN	6.59	6.75	6.57	6.17
SD	0.322	0.457	0.585	0.477
N	8	8	8	8
Period: Week 18				
MEAN	7.04	7.06	6.86	6.10
SD	0.280	0.134	0.857	0.998
N	4	4	4	4
Period: Week 26				
MEAN	7.07	6.69	7.03	6.95
SD	0.298	0.810	0.522	0.681
N	4	4	4	4

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Hemoglobin

STUDY ID: 097
STUDY NO: 097
ABBR: THGB

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	15.0	15.3	15.6	15.7	
SD	1.22	0.97	0.74	1.03	
N	8	8	8	8	
Period: Week -1					
MEAN	15.4	15.3	15.1	16.1	
SD	1.60	0.80	1.17	0.81	
N	8	8	8	8	
Period: Week 2					
MEAN	14.9	15.2	15.5	15.5	
SD	1.57	1.46	1.08	1.30	
N	8	8	8	8	
Period: Week 4					
MEAN	15.5	15.5	14.0*	13.5*	
SD	0.97	0.82	1.12	1.36	
N	8	8	8	8	
Period: Week 8					
MEAN	15.6	16.3	15.7	15.7	
SD	0.72	0.92	1.24	1.42	
N	8	8	8	8	
Period: Week 13					
MEAN	15.8	16.4	15.2	14.9	
SD	1.30	1.45	1.50	1.68	
N	8	8	8	8	
Period: Week 18					
MEAN	17.0	16.4	17.9	16.0	
SD	1.20	0.43	1.57	2.01	
N	4	4	4	4	
Period: Week 26					
MEAN	17.9	17.1	17.9	17.7	
SD	0.26	1.48	1.46	1.00	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Hemoglobin

STUDY ID: 097
STUDY NO: 097
ABBR: THGB

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0
				mg base/kg/day
Period: Week -3				
MEAN	15.7	15.7	15.6	15.8
SD	0.95	0.90	0.86	0.62
N	8	8	8	8
Period: Week -1				
MEAN	15.5	15.3	16.0	15.3
SD	0.94	0.88	1.24	1.42
N	8	8	8	8
Period: Week 2				
MEAN	15.7	15.3	15.6	14.7
SD	0.73	1.16	1.06	0.88
N	8	8	8	8
Period: Week 4				
MEAN	15.6	15.6	14.4*	13.1*
SD	0.88	0.66	1.13	1.09
N	8	8	8	8
Period: Week 8				
MEAN	15.9	16.3	15.9	15.4
SD	1.45	1.30	1.47	1.05
N	8	8	8	8
Period: Week 13				
MEAN	16.5	16.7	16.0	15.4
SD	0.87	1.05	1.53	1.28
N	8	8	8	8
Period: Week 18				
MEAN	17.6	17.5	17.2	15.5
SD	0.93	0.73	2.32	2.38
N	4	4	4	4
Period: Week 26				
MEAN	17.8	16.5	17.4	17.4
SD	1.18	1.81	1.23	1.71
N	4	4	4	4

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Hematocrit

STUDY ID: 097
STUDY NO: 097
ABBR: HCT

SEX: MALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	43.9	44.9	45.8	45.5
SD	3.16	2.74	2.57	2.71
N	8	8	8	8
Period: Week -1				
MEAN	44.7	44.2	43.9	45.9
SD	4.10	2.23	3.38	2.30
N	8	8	8	8
Period: Week 2				
MEAN	43.1	43.6	44.3	44.0
SD	3.81	3.75	3.10	3.32
N	8	8	8	8
Period: Week 4				
MEAN	44.3	44.1	41.0	39.7*
SD	2.54	2.10	3.23	3.30
N	8	8	8	8
Period: Week 8				
MEAN	43.3	45.0	44.6	44.3
SD	1.33	3.14	3.48	2.99
N	8	8	8	8
Period: Week 13				
MEAN	44.9	46.4	43.8	42.2
SD	3.37	4.15	4.16	4.08
N	8	8	8	8
Period: Week 18				
MEAN	48.1	45.8	51.1	45.6
SD	3.12	1.79	4.14	5.38
N	4	4	4	4
Period: Week 26				
MEAN	50.6	48.1	49.7	48.9
SD	1.22	4.34	3.22	2.46
N	4	4	4	4

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Hematocrit

STUDY ID: 097
STUDY NO: 097
ABBR: HCT

SEX: FEMALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	45.8	45.9	45.7	46.0
SD	2.59	2.52	2.83	1.40
N	8	8	8	8
Period: Week -1				
MEAN	44.9	44.4	46.0	43.9
SD	2.75	2.07	3.52	4.32
N	8	8	8	8
Period: Week 2				
MEAN	44.8	43.9	44.7	41.9
SD	2.30	2.72	3.19	2.45
N	8	8	8	8
Period: Week 4				
MEAN	44.5	44.3	42.1	38.8*
SD	2.51	1.73	2.69	2.79
N	8	8	8	8
Period: Week 8				
MEAN	44.4	44.8	44.5	44.1
SD	2.47	2.83	3.95	2.89
N	8	8	8	8
Period: Week 13				
MEAN	46.2	47.2	46.0	44.2
SD	2.34	3.41	4.68	3.36
N	8	8	8	8
Period: Week 18				
MEAN	49.4	49.0	48.2	44.8
SD	2.62	1.75	7.04	6.32
N	4	4	4	4
Period: Week 26				
MEAN	49.9	46.1	48.5	49.0
SD	3.25	5.24	3.68	4.19
N	4	4	4	4

*-Significant Difference from Control P < .05

Table 8.7

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Mean Corpuscular Volume

STUDY ID: 097
STUDY NO: 097
ABBR: MCV

SEX: MALE

UNITS: fL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	71.5	70.8	69.9	70.9	
SD	1.06	2.22	3.05	3.00	
N	8	8	8	8	
Period: Week -1					
MEAN	70.9	70.2	69.4	70.4	
SD	1.05	1.88	2.90	2.81	
N	8	8	8	8	
Period: Week 2					
MEAN	70.6	69.8	69.2	70.5	
SD	1.45	1.95	2.83	3.29	
N	8	8	8	8	
Period: Week 4					
MEAN	70.6	69.8	71.8	73.1	
SD	1.09	1.69	2.91	3.32	
N	8	8	8	8	
Period: Week 8					
MEAN	70.4	69.7	70.7	69.3	
SD	1.03	1.61	2.64	2.96	
N	8	8	8	8	
Period: Week 13					
MEAN	70.9	70.0	69.8	69.5	
SD	1.24	2.10	2.80	4.41	
N	8	8	8	8	
Period: Week 18					
MEAN	69.6	69.1	67.4	67.9	
SD	0.73	2.10	1.77	4.99	
N	4	4	4	4	
Period: Week 26					
MEAN	69.7	69.0	65.9	65.6	
SD	0.88	2.57	1.75	3.39	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Mean Corpuscular Volume

STUDY ID: 097
STUDY NO: 097
ABBR: MCV

SEX: FEMALE

UNITS: fL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	71.6	70.3	70.5	72.5
SD	1.29	2.16	1.67	2.60
N	8	8	8	8
Period: Week -1				
MEAN	70.6	69.7	70.4	71.8
SD	1.14	2.08	1.41	2.58
N	8	8	8	8
Period: Week 2				
MEAN	70.1	69.4	70.3	71.7
SD	1.80	1.92	1.64	2.43
N	8	8	8	8
Period: Week 4				
MEAN	70.5	69.4	72.7	73.8*
SD	1.56	1.66	2.00	3.05
N	8	8	8	8
Period: Week 8				
MEAN	69.9	69.2	71.1	71.6
SD	1.34	2.13	1.95	2.57
N	8	8	8	8
Period: Week 13				
MEAN	70.2	69.9	69.9	71.8
SD	1.18	2.48	2.24	3.59
N	8	8	8	8
Period: Week 18				
MEAN	70.2	69.4	70.1	73.7*
SD	1.25	1.33	1.64	1.92
N	4	4	4	4
Period: Week 26				
MEAN	70.5	68.9	69.0	70.6
SD	1.83	1.51	1.32	1.48
N	4	4	4	4

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Mean Corpuscular Hemoglobin

STUDY ID: 097
STUDY NO: 097
ABBR: TMCH

SEX: MALE

UNITS: pg

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	24.4	24.1	23.8	24.5	
SD	0.42	0.70	1.05	1.15	
N	8	8	8	8	
Period: Week -1					
MEAN	24.4	24.3	24.0	25.0	
SD	0.40	0.59	1.01	1.08	
N	8	8	8	8	
Period: Week 2					
MEAN	24.4	24.3	24.2	24.9	
SD	0.62	0.64	0.91	0.95	
N	8	8	8	8	
Period: Week 4					
MEAN	24.7	24.5	24.5	24.8	
SD	0.48	0.65	0.77	1.11	
N	8	8	8	8	
Period: Week 8					
MEAN	25.4	25.3	25.0	24.5	
SD	1.05	0.87	1.55	1.04	
N	8	8	8	8	
Period: Week 13					
MEAN	24.9	24.8	24.2	24.2	
SD	0.49	0.73	1.02	1.38	
N	8	8	8	8	
Period: Week 18					
MEAN	24.6	24.8	23.6	23.7	
SD	0.51	0.61	0.87	1.58	
N	4	4	4	4	
Period: Week 26					
MEAN	24.6	24.5	23.7	23.7	
SD	0.59	0.74	0.91	1.31	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Mean Corpuscular Hemoglobin

STUDY ID: 097
STUDY NO: 097
ABBR: TMCH

SEX: FEMALE

UNITS: pg

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	24.5	24.1	24.1	24.9	
SD	0.57	1.05	0.76	1.05	
N	8	8	8	8	
Period: Week -1					
MEAN	24.3	24.0	24.5	25.0	
SD	0.38	1.00	0.57	0.86	
N	8	8	8	8	
Period: Week 2					
MEAN	24.6	24.4	24.5	25.1	
SD	0.54	1.17	0.74	1.02	
N	8	8	8	8	
Period: Week 4					
MEAN	24.7	24.4	24.9	24.9	
SD	0.74	0.84	0.77	1.04	
N	8	8	8	8	
Period: Week 8					
MEAN	25.3	25.2	25.4	25.0	
SD	1.21	1.44	1.14	0.75	
N	8	8	8	8	
Period: Week 13					
MEAN	25.1	24.7	24.4	24.9	
SD	0.46	0.89	0.98	0.98	
N	8	8	8	8	
Period: Week 18					
MEAN	24.9	24.8	25.0	25.5	
SD	0.47	0.61	0.50	0.41	
N	4	4	4	4	
Period: Week 26					
MEAN	25.1	24.7	24.8	25.1	
SD	0.79	0.57	0.54	0.45	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Mean Copuscular Hemo. Conc.

STUDY ID: 097
STUDY NO: 097
ABBR: TMCHC

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	34.1	34.1	34.0	34.6	
SD	0.54	0.64	0.41	0.50	
N	8	8	8	8	
Period: Week -1					
MEAN	34.5	34.6	34.5	35.0	
SD	0.51	0.51	0.33	0.30	
N	8	8	8	8	
Period: Week 2					
MEAN	34.6	34.8	35.0	35.2	
SD	0.62	0.64	0.74	0.70	
N	8	8	8	8	
Period: Week 4					
MEAN	35.0	35.1	34.1*	34.0*	
SD	0.34	0.38	0.64	0.85	
N	8	8	8	8	
Period: Week 8					
MEAN	36.0	36.3	35.3	35.3	
SD	1.22	1.22	1.59	1.53	
N	8	8	8	8	
Period: Week 13					
MEAN	35.2	35.4	34.6	34.9	
SD	0.43	0.28	0.65	0.60	
N	8	8	8	8	
Period: Week 18					
MEAN	35.3	35.8	35.0	35.0	
SD	0.39	0.46	0.76	0.77	
N	4	4	4	4	
Period: Week 26					
MEAN	35.3	35.6	35.9	36.2	
SD	0.43	0.42	0.67	0.25	
N	4	4	4	4	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Mean Copuscular Hemo. Conc.

STUDY ID: 097
STUDY NO: 097
ABBR: TMCHC

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	34.2	34.2	34.2	34.4	
SD	0.33	0.64	0.63	0.68	
N	8	8	8	8	
Period: Week -1					
MEAN	34.5	34.5	34.7	34.9	
SD	0.71	0.61	0.33	0.72	
N	8	8	8	8	
Period: Week 2					
MEAN	35.1	35.0	34.9	35.0	
SD	0.66	0.65	0.60	0.47	
N	8	8	8	8	
Period: Week 4					
MEAN	35.1	35.1	34.2	33.8*	
SD	0.60	0.61	0.69	0.87	
N	8	8	8	8	
Period: Week 8					
MEAN	36.2	36.4	35.7	34.9	
SD	1.58	1.23	1.39	1.15	
N	8	8	8	8	
Period: Week 13					
MEAN	35.7	35.4	34.9	34.7*	
SD	0.43	1.04	0.54	0.89	
N	8	8	8	8	
Period: Week 18					
MEAN	35.5	35.7	35.7	34.6	
SD	0.08	0.22	0.62	1.00	
N	4	4	4	4	
Period: Week 26					
MEAN	35.6	35.8	35.9	35.5	
SD	0.36	0.39	0.28	0.55	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Reticulocyte Count

STUDY ID: 097
STUDY NO: 097
ABBR: RETICS

SEX: MALE

UNITS: % RBCs

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.4	0.4	0.5	0.3	
SD	0.20	0.40	0.34	0.15	
N	8	8	8	8	
Period: Week -1					
MEAN	0.2	0.1	0.1	0.1	
SD	0.16	0.07	0.13	0.07	
N	8	8	8	8	
Period: Week 2					
MEAN	0.1	0.2	0.4	0.3	
SD	0.20	0.17	0.23	0.18	
N	8	8	8	8	
Period: Week 4					
MEAN	0.3	0.1	0.6	1.1*	
SD	0.22	0.21	0.18	0.48	
N	8	8	8	8	
Period: Week 8					
MEAN	0.2	0.3	0.7	0.9*	
SD	0.29	0.16	0.24	0.71	
N	8	8	8	8	
Period: Week 13					
MEAN	0.3	0.3	0.8*	1.2*	
SD	0.18	0.35	0.34	0.39	
N	8	8	8	8	
Period: Week 18					
MEAN	0.5	0.6	0.6	0.8	
SD	0.17	0.34	0.13	0.31	
N	4	4	4	4	
Period: Week 26					
MEAN	0.3	0.4	0.4	0.4	
SD	0.15	0.29	0.35	0.31	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Reticulocyte Count

STUDY ID: 097
STUDY NO: 097
ABBR: RETICS

SEX: FEMALE

UNITS: % RBCs

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.3	0.3	0.2	0.4	
SD	0.21	0.09	0.24	0.25	
N	8	8	8	8	
Period: Week -1					
MEAN	0.1	D.1	0.1	0.2	
SD	0.14	0.10	0.05	0.18	
N	8	8	8	8	
Period: Week 2					
MEAN	0.2	0.3	0.3	0.5	
SD	0.19	0.21	0.23	0.43	
N	8	8	8	8	
Period: Week 4					
MEAN	0.2	0.1	0.7*	0.7*	
SD	0.15	0.16	0.37	0.42	
N	8	8	8	8	
Period: Week 8					
MEAN	0.1	0.2	0.8*	0.9*	
SD	0.11	0.19	0.43	0.40	
N	8	8	8	8	
Period: Week 13					
MEAN	0.4	0.3	0.6	1.3*	
SD	0.18	0.16	0.36	0.34	
N	8	8	8	8	
Period: Week 18					
MEAN	0.4	0.3	0.5	0.6	
SD	D.29	0.15	0.41	0.46	
N	4	4	4	4	
Period: Week 26					
MEAN	0.6	0.4	0.2	0.2	
SD	D.19	D.38	D.22	0.06	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Nucleated Red Cells

STUDY ID: 097
STUDY NO: 097
ABBR: NRBC

SEX: MALE

UNITS: COUNT

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0	0	0	0	
SD	0.4	0.4	0.7	0.4	
N	8	8	8	8	
Period: Week -1					
MEAN	0	0	0	0	
SD	0.0	0.0	0.4	0.0	
N	8	8	8	8	
Period: Week 2					
MEAN	0	0	0	1	
SD	0.5	0.5	0.4	1.6	
N	8	8	8	8	
Period: Week 4					
MEAN	0	1	1	5*	
SD	0.4	1.4	0.8	3.0	
N	8	8	8	8	
Period: Week 8					
MEAN	0	1	1	2	
SD	0.7	1.2	0.8	3.1	
N	8	8	8	8	
Period: Week 13					
MEAN	1	1	1	1	
SD	0.8	2.4	0.5	1.4	
N	8	8	8	8	
Period: Week 18					
MEAN	1	1	1	0	
SD	2.0	1.5	1.0	0.0	
N	4	4	4	4	
Period: Week 26					
MEAN	2	0	4	1	
SD	2.4	0.5	5.1	0.6	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Nucleated Red Cells

STUDY IO: 097
STUDY NO: 097
ABBR: NRBC

SEX: FEMALE

UNITS: COUNT

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0	0	0	0	
SD	0.0	0.4	0.5	0.5	
N	8	8	8	8	
Period: Week -1					
MEAN	0	0	0	0	
SD	0.4	0.0	0.7	0.0	
N	8	8	8	8	
Period: Week 2					
MEAN	0	0	1	1	
SD	0.0	0.0	1.4	1.1	
N	8	8	8	8	
Period: Week 4					
MEAN	0	0	2	5*	
SD	0.4	1.1	1.7	3.7	
N	8	8	8	8	
Period: Week 8					
MEAN	0	0	1	1	
SD	0.7	0.7	1.1	1.8	
N	8	8	8	8	
Period: Week 13					
MEAN	1	0	0	2	
SD	0.9	0.4	0.4	2.9	
N	8	8	8	8	
Period: Week 18					
MEAN	1	1	0	0	
SD	0.6	1.3	0.0	0.5	
N	4	4	4	4	
Period: Week 26					
MEAN	0	0	1	0	
SD	0.0	0.5	1.0	0.0	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Heinz Bodies

STUDY ID: 097
STUOY NO: 097
ABBR: HB

SEX: MALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.2	0.0	0.2	0.0	
SD	0.26	0.07	0.28	0.07	
N	8	8	8	8	
Period: Week -1					
MEAN	0.0	0.0	0.0	0.0	
SO	0.04	0.04	0.05	0.05	
N	8	8	8	8	
Period: Week 2					
MEAN	0.0	0.0	0.1	0.0	
SD	0.00	0.04	0.14	0.05	
N	8	8	8	8	
Period: Week 4					
MEAN	0.0	0.0	0.1	0.0	
SD	0.00	0.07	0.12	0.11	
N	8	8	8	8	
Period: Week 8					
MEAN	0.1	0.1	0.1	0.1	
SD	0.11	0.08	0.08	0.11	
N	8	8	8	8	
Period: Week 13					
MEAN	0.3	0.4	0.1	0.1	
SD	0.37	0.35	0.10	0.18	
N	8	8	8	8	
Period: Week 18					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.05	0.05	0.00	
N	4	4	4	4	
Period: Week 26					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.05	0.00	0.00	
N	4	4	4	4	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Heinz Bodies

STUDY ID: 097
STUDY NO: 097
ABBR: HB

SEX: FEMALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.2	0.2	0.1	0.2	
SD	0.29	0.20	0.11	0.15	
N	8	8	8	8	
Period: Week -1					
MEAN	0.0	0.1	0.0	0.0	
SD	0.05	0.11	0.05	0.04	
N	8	8	8	8	
Period: Week 2					
MEAN	0.0	0.1	0.0	0.1	
SD	0.00	0.14	0.00	0.19	
N	8	8	8	8	
Period: Week 4					
MEAN	0.0	0.0	0.0	0.0	
SD	0.07	0.00	0.05	0.07	
N	8	8	8	8	
Period: Week 8					
MEAN	0.1	0.1	0.2	0.1	
SD	0.15	0.11	0.29	0.05	
N	8	8	8	8	
Period: Week 13					
MEAN	0.1	0.3	0.2	0.2	
SD	0.12	0.27	0.21	0.31	
N	8	8	8	8	
Period: Week 18					
MEAN	0.1	0.1	0.0	0.0	
SD	0.06	0.10	0.00	0.00	
N	4	4	4	4	
Period: Week 26					
MEAN	0.0	0.1	0.0	0.0	
SD	0.00	0.10	0.05	0.00	
N	4	4	4	4	

Table 8.19

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

DRAFT

SUMMARY OF HEMATOLOGICAL TESTS
TEST: % Methemoglobin

STUDY ID: 097
STUDY NO: 097
ABBR: %METHGB

SEX: MALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	1.9	2.1	2.0	1.8	
SD	0.91	1.03	0.75	0.47	
N	8	8	8	8	
Period: Week -1					
MEAN	1.3	1.4	1.6	1.5	
SD	0.44	0.63	0.70	0.68	
N	8	8	8	8	
Period: Week 2					
MEAN	0.9	1.2	13.0*	16.8*	
SD	0.20	0.44	3.58	6.23	
N	8	8	8	8	
Period: Week 4					
MEAN	0.9	1.1	14.8*	17.5*	
SD	0.21	0.29	3.67	4.95	
N	8	8	8	8	
Period: Week 8					
MEAN	1.0	0.9	13.6*	18.8*	
SD	0.30	0.16	4.25	4.75	
N	8	8	8	8	
Period: Week 13					
MEAN	0.8	1.2	12.9*	17.8*	
SD	0.24	0.63	3.96	6.67	
N	8	8	8	8	
Period: Week 18					
MEAN	0.7	0.7	0.8	3.8*	
SD	0.12	0.14	0.40	1.40	
N	4	4	4	4	
Period: Week 26					
MEAN	0.7	0.9	0.8	0.9	
SD	0.17	0.06	0.14	0.13	
N	4	4	4	4	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: % Methemoglobin

STUDY ID: 097
STUDY NO: 097
ABBR: %METHGB

SEX: FEMALE

UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	1.8	2.1	2.0	1.4	
SD	0.73	1.19	1.25	0.41	
N	8	8	8	8	
Period: Week -1					
MEAN	1.4	1.7	1.4	1.1	
SD	0.77	1.24	0.78	0.41	
N	8	8	8	8	
Period: Week 2					
MEAN	1.0	1.4	11.7*	24.0*	
SD	0.39	0.72	4.82	6.43	
N	8	8	8	8	
Period: Week 4					
MEAN	1.1	1.0	14.7*	22.8*	
SD	0.46	0.20	2.93	4.82	
N	8	8	8	8	
Period: Week 8					
MEAN	0.8	1.1	12.5*	23.6*	
SD	0.08	0.26	2.29	4.26	
N	8	8	8	8	
Period: Week 13					
MEAN	0.9	1.7	12.9*	24.8*	
SD	0.20	1.21	2.47	5.19	
N	8	8	8	8	
Period: Week 18					
MEAN	0.7	0.7	1.0	4.2*	
SD	0.32	0.17	0.22	1.95	
N	4	4	4	4	
Period: Week 26					
MEAN	0.9	1.0	1.0	1.1	
SD	0.22	0.10	0.10	0.15	
N	4	4	4	4	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Platelets

STUDY ID: 097
STUDY NO: 097
ABBR: PLT

SEX: MALE

UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	356	387	416	371
SD	74.1	59.5	96.1	79.6
N	8	8	8	8
Period: Week -1				
MEAN	298	336	360	316
SD	67.8	38.1	64.8	64.2
N	8	8	8	8
Period: Week 2				
MEAN	246	278	147*	98*
SD	56.9	53.5	60.0	15.4
N	8	8	8	8
Period: Week 4				
MEAN	256	287	113*	92*
SD	58.0	54.0	42.5	37.4
N	8	8	8	8
Period: Week 8				
MEAN	240	266	159	217
SD	48.6	42.8	75.8	105.9
N	8	8	8	8
Period: Week 13				
MEAN	241	281	185	222
SD	47.7	32.9	91.9	150.0
N	8	8	8	8
Period: Week 18				
MEAN	260	315	343	314
SD	36.8	15.6	61.3	141.3
N	4	4	4	4
Period: Week 26				
MEAN	251	312	288	286
SD	39.2	26.6	82.2	25.5
N	4	4	4	4

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Platelets

STUDY ID: 097
STUDY NO: 097
ABBR: PLT

SEX: FEMALE

UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	371	358	346	396	
SD	101.1	97.3	70.2	86.7	
N	8	8	8	8	
Period: Week -1					
MEAN	317	309	333	337	
SD	76.2	114.0	49.0	74.2	
N	8	8	8	8	
Period: Week 2					
MEAN	270	276	155*	84*	
SD	54.4	54.0	60.0	32.9	
N	8	8	8	8	
Period: Week 4					
MEAN	297	254	128*	153*	
SD	53.6	60.2	42.6	92.6	
N	8	8	8	8	
Period: Week 8					
MEAN	287	258	210	213	
SD	33.6	40.0	96.5	103.0	
N	8	8	8	8	
Period: Week 13					
MEAN	303	264	262	244	
SD	43.1	41.7	85.1	114.6	
N	8	8	8	8	
Period: Week 18					
MEAN	318	341	372	235	
SD	42.6	81.7	74.2	73.1	
N	4	4	4	4	
Period: Week 26					
MEAN	286	345	321	295	
SD	25.5	167.0	76.0	91.3	
N	4	4	4	4	

*-Significant Difference from Control P < .05

Table 8.23

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Prothrombin Time

STUDY ID: 097
STUDY NO: 097
ABBR: PT

SEX: MALE

UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	7.2	7.3	7.3	7.3	
SD	0.41	0.27	0.19	0.13	
N	8	8	8	8	
Period: Week -1					
MEAN	7.3	7.3	7.2	7.2	
SD	0.37	0.33	0.12	0.12	
N	8	8	8	8	
Period: Week 2					
MEAN	7.4	7.5	7.2	7.1	
SD	0.41	0.27	0.17	0.05	
N	8	8	8	8	
Period: Week 4					
MEAN	7.2	7.2	6.9*	6.9*	
SD	0.33	0.19	0.10	0.09	
N	8	8	8	8	
Period: Week 8					
MEAN	7.2	7.5	7.1	7.2	
SD	0.17	0.30	0.13	0.36	
N	8	8	8	8	
Period: Week 13					
MEAN	7.3	7.3	7.1	7.0	
SD	0.30	0.27	0.14	0.10	
N	8	8	8	8	
Period: Week 18					
MEAN	7.2	7.4	7.4	7.1	
SD	0.39	0.41	0.10	0.10	
N	4	4	4	4	
Period: Week 26					
MEAN	7.6	7.6	7.5	7.4	
SD	0.53	0.32	0.10	0.08	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Prothrombin Time

STUDY ID: 097
STUDY NO: 097
ABBR: PT

SEX: FEMALE

UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	7.2	7.2	7.2	7.2	
SD	0.16	0.20	0.18	0.17	
N	8	8	8	8	
Period: Week -1					
MEAN	7.3	7.3	7.4	7.3	
SD	0.14	0.23	0.20	0.18	
N	8	8	8	8	
Period: Week 2					
MEAN	7.3	7.4	7.2	7.1	
SD	0.25	0.24	0.19	0.20	
N	8	8	8	8	
Period: Week 4					
MEAN	7.2	7.3	6.9*	6.9*	
SD	0.17	0.18	0.09	0.19	
N	8	8	8	8	
Period: Week 8					
MEAN	7.2	7.3	7.2	7.3	
SD	0.29	0.34	0.23	0.24	
N	8	8	8	8	
Period: Week 13					
MEAN	7.3	7.3	7.1	7.1	
SD	0.21	0.24	0.17	0.20	
N	8	8	8	8	
Period: Week 18					
MEAN	7.3	7.3	7.2	7.3	
SD	0.10	0.30	0.22	0.13	
N	4	4	4	4	
Period: Week 26					
MEAN	7.4	7.4	7.4	7.5	
SD	0.28	0.08	0.15	0.25	
N	4	4	4	4	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Act. Partial Thrombo. Time

STUDY ID: 097
STUDY NO: 097
ABBR: APTT

SEX: MALE

UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	12.1	12.0	11.5	11.8	
SD	0.49	1.04	0.35	0.48	
N	8	8	8	8	
Period: Week -1					
MEAN	11.5	11.5	11.3	11.5	
SD	0.45	0.72	0.77	0.53	
N	8	8	8	8	
Period: Week 2					
MEAN	10.8	11.0	10.5	10.6	
SD	0.52	0.90	0.31	0.45	
N	8	8	8	8	
Period: Week 4					
MEAN	10.6	10.8	10.5	11.2	
SD	0.43	1.03	0.37	0.14	
N	8	8	8	8	
Period: Week 8					
MEAN	10.5	10.7	10.2	10.4	
SD	0.87	0.82	0.34	0.32	
N	8	8	8	8	
Period: Week 13					
MEAN	10.6	10.6	10.4	10.9	
SD	0.40	0.92	0.40	0.52	
N	8	8	8	8	
Period: Week 18					
MEAN	10.8	10.5	10.2	10.6	
SD	0.34	0.26	0.26	0.19	
N	4	4	4	4	
Period: Week 26					
MEAN	10.8	11.1	10.4	10.6	
SD	0.34	0.88	0.10	0.10	
N	4	4	4	4	

Table 8.26

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

DRAFT

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Act. Partial Thrombo. Time

STUDY ID: 097
STUDY NO: 097
ABBR: APTT

SEX: FEMALE

UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	12.0	11.9	11.6	11.9	
SD	0.60	0.64	0.60	0.54	
N	8	8	8	8	
Period: Week -1					
MEAN	12.2	11.8	11.4	12.0	
SD	0.85	0.81	0.56	0.75	
N	8	8	8	8	
Period: Week 2					
MEAN	11.4	11.2	10.9	11.2	
SD	0.93	0.74	0.57	0.70	
N	8	8	8	8	
Period: Week 4					
MEAN	11.0	10.7	10.8	11.7	
SD	0.77	0.41	0.74	0.63	
N	8	8	8	8	
Period: Week 8					
MEAN	10.7	10.9	10.4	10.8	
SD	0.49	0.47	0.58	0.59	
N	8	8	8	8	
Period: Week 13					
MEAN	10.8	11.0	10.7	11.1	
SD	0.48	0.69	0.47	1.60	
N	8	8	8	8	
Period: Week 18					
MEAN	10.3	10.7	10.5	11.2	
SD	0.17	0.38	0.40	1.16	
N	4	4	4	4	
Period: Week 26					
MEAN	10.7	11.0	10.7	11.4	
SD	0.32	0.52	0.70	0.81	
N	4	4	4	4	

Table 8.27

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Leukocytes

STUDY ID: 097
STUDY NO: 097
ABBR: WBC

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	8.6	9.5	9.2	8.5
SD	1.51	2.57	1.48	1.81
N	8	8	8	8
Period: Week -1				
MEAN	8.2	10.2	8.8	9.6
SD	2.03	2.23	2.01	1.12
N	8	8	8	8
Period: Week 2				
MEAN	9.0	10.0	10.6	8.9
SD	3.40	3.00	2.84	1.05
N	8	8	8	8
Period: Week 4				
MEAN	9.1	8.7	10.6	9.7
SD	2.14	1.82	1.44	2.08
N	8	8	8	8
Period: Week 8				
MEAN	8.3	9.0	10.0	11.3*
SD	1.59	2.02	1.45	2.05
N	8	8	8	8
Period: Week 13				
MEAN	8.4	8.7	11.4*	13.0*
SD	1.83	1.60	1.25	3.04
N	8	8	8	8
Period: Week 18				
MEAN	9.5	9.0	7.4	9.5
SD	2.09	1.12	1.44	0.76
N	4	4	4	4
Period: Week 26				
MEAN	9.8	10.2	8.6	8.2
SD	1.56	0.79	1.13	0.53
N	4	4	4	4

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Leukocytes

STUDY ID: 097
STUDY NO: 097
ABBR: WBC

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0 mg base/kg/day
Period: Week -3				
MEAN	8.2	8.4	7.8	8.5
SD	1.54	1.21	2.03	1.29
N	8	8	8	8
Period: Week -1				
MEAN	8.7	9.9	8.8	9.8
SD	2.39	2.30	2.06	2.54
N	8	8	8	8
Period: Week 2				
MEAN	9.5	9.5	8.0	8.5
SD	3.06	1.89	1.72	1.82
N	8	8	8	8
Period: Week 4				
MEAN	7.6	8.4	9.0	8.3
SD	1.62	2.25	2.20	1.05
N	8	8	8	8
Period: Week 8				
MEAN	7.6	8.7	10.3	10.2
SD	0.92	2.58	2.56	3.62
N	8	8	8	8
Period: Week 13				
MEAN	8.4	8.1	11.2	13.6*
SD	2.27	1.57	3.85	5.57
N	8	8	8	8
Period: Week 18				
MEAN	6.4	8.6	8.9	10.6
SD	1.14	2.47	2.16	7.60
N	4	4	4	4
Period: Week 26				
MEAN	7.8	9.5	8.9	9.0
SD	1.46	2.54	3.19	1.16
N	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: M. Neutrophils

STUDY ID: 097
STUDY NO: 097
ABBR: M. Neutrop

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	4.8	5.4	5.5	4.9	
SD	0.86	1.76	1.21	0.96	
N	8	8	8	8	
Period: Week -1					
MEAN	5.2	6.6	5.4	5.9	
SD	1.66	2.16	1.55	0.71	
N	8	8	8	8	
Period: Week 2					
MEAN	5.8	6.2	7.0	5.5	
SD	2.82	2.41	2.19	1.36	
N	8	8	8	8	
Period: Week 4					
MEAN	6.1	4.7	6.8	6.2	
SD	1.56	1.35	1.31	1.90	
N	8	8	8	8	
Period: Week 8					
MEAN	5.1	5.2	6.0	7.6*	
SD	0.89	1.61	1.31	2.10	
N	8	8	8	8	
Period: Week 13					
MEAN	5.1	5.1	7.7*	9.2*	
SD	1.13	1.08	0.86	2.35	
N	8	8	8	8	
Period: Week 18					
MEAN	6.0	5.4	4.2	6.1	
SD	1.10	1.34	1.26	0.86	
N	4	4	4	4	
Period: Week 26					
MEAN	6.4	7.0	5.5	5.0	
SD	1.04	1.45	1.03	0.78	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.30

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: M. Neutrophils

STUDY ID: 097
STUDY NO: 097
ABBR: M. Neutrop

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	5.0	4.9	4.3	4.9	
SD	1.06	0.99	1.45	1.26	
N	8	8	8	8	
Period: Week -1					
MEAN	5.8	6.3	5.0	6.8	
SD	1.74	1.84	2.15	2.47	
N	8	8	8	8	
Period: Week 2					
MEAN	6.4	5.9	4.8	5.4	
SD	2.66	1.82	1.25	2.03	
N	8	8	8	8	
Period: Week 4					
MEAN	4.5	5.0	5.4	5.3	
SD	0.87	2.05	1.54	1.32	
N	8	8	8	8	
Period: Week 8					
MEAN	4.7	4.9	6.9	7.2	
SD	0.50	1.98	2.53	3.60	
N	8	8	8	8	
Period: Week 13					
MEAN	5.3	4.7	8.1	9.1*	
SD	1.56	0.99	3.28	3.09	
N	8	8	8	8	
Period: Week 18					
MEAN	3.3	5.3	5.9	6.7	
SD	0.71	2.36	2.13	4.55	
N	4	4	4	4	
Period: Week 26					
MEAN	4.8	6.2	5.7	5.3	
SD	0.88	2.11	2.27	0.77	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: I. Neutrophils

STUDY ID: 097
STUDY NO: 097
ABBR: I. Neutrop

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.1	0.1	0.1	0.1	
SD	0.09	0.05	0.11	0.07	
N	8	8	8	8	
Period: Week -1					
MEAN	0.2	0.2	0.2	0.1	
SD	0.05	0.15	0.16	0.08	
N	8	8	8	8	
Period: Week 2					
MEAN	0.3	0.4	0.4	0.3	
SD	0.21	0.10	0.29	0.12	
N	8	8	8	8	
Period: Week 4					
MEAN	0.4	0.4	0.7	0.5	
SD	0.25	0.18	0.31	0.18	
N	8	8	8	8	
Period: Week 8					
MEAN	0.3	0.3	0.4	0.5	
SD	0.12	0.11	0.30	0.21	
N	8	8	8	8	
Period: Week 13					
MEAN	0.3	0.2	0.3	0.4	
SD	0.24	0.16	0.32	0.27	
N	8	8	8	8	
Period: Week 18					
MEAN	0.2	0.2	0.4	0.2	
SD	0.14	0.15	0.25	0.06	
N	4	4	4	4	
Period: Week 26					
MEAN	0.2	0.2	0.2	0.2	
SD	0.10	0.15	0.19	0.10	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

Table 8.32

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

DRAFT

SUMMARY OF HEMATOLOGICAL TESTS
TEST: I. Neutrophils

STUDY ID: 097
STUDY NO: 097
ABBR: I. Neutrop

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.5	0.1	0.1	0.1	
SD	1.25	0.09	0.06	0.07	
N	8	8	8	8	
Period: Week -1					
MEAN	0.1	0.1	0.2	0.1	
SD	0.12	0.13	0.14	0.13	
N	8	8	8	8	
Period: Week 2					
MEAN	0.2	0.2	0.3	0.5	
SD	0.15	0.17	0.20	0.43	
N	8	8	8	8	
Period: Week 4					
MEAN	0.2	0.3	0.5	0.5*	
SD	0.20	0.29	0.27	0.23	
N	8	8	8	8	
Period: Week 8					
MEAN	0.2	0.2	0.6*	0.3	
SD	0.10	0.13	0.47	0.15	
N	8	8	8	8	
Period: Week 13					
MEAN	0.1	0.3	0.4	0.9	
SD	0.10	0.18	0.40	1.46	
N	8	8	8	8	
Period: Week 18					
MEAN	0.2	0.2	0.3	0.8	
SD	0.06	0.17	0.17	1.22	
N	4	4	4	4	
Period: Week 26					
MEAN	0.0	0.3	0.2	0.2	
SD	0.05	0.25	0.26	0.10	
N	4	4	4	4	

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05

Table 8.33

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Lymphocytes

STUDY ID: 097
STUDY NO: 097
ABBR: Lymphocyte

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	3.0	3.0	2.8	2.8	
SD	0.62	1.08	0.62	0.76	
N	8	8	8	8	
Period: Week -1					
MEAN	2.3	2.6	2.6	2.7	
SD	0.53	0.71	0.62	0.94	
N	8	8	8	8	
Period: Week 2					
MEAN	2.3	2.5	2.3	2.3	
SD	0.53	0.52	0.68	0.70	
N	8	8	8	8	
Period: Week 4					
MEAN	2.0	2.7	2.1	1.9	
SD	0.76	0.69	0.81	0.55	
N	8	8	8	8	
Period: Week 8					
MEAN	2.4	2.5	2.5	1.9	
SD	0.86	0.70	0.68	0.80	
N	8	8	8	8	
Period: Week 13					
MEAN	2.1	2.4	2.2	1.9	
SD	0.61	0.66	0.68	0.38	
N	8	8	8	8	
Period: Week 18					
MEAN	2.5	2.6	2.0	2.0	
SD	0.71	0.59	0.33	0.78	
N	4	4	4	4	
Period: Week 26					
MEAN	2.6	2.1	2.1	2.3	
SD	0.40	0.56	0.61	0.68	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Lymphocytes

STUDY ID: 097
STUDY NO: 097
ABBR: Lymphocyte

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	2.2	2.9	2.8	2.6	
SD	1.20	0.53	0.89	0.89	
N	8	8	8	8	
Period: Week -1					
MEAN	2.2	2.9	3.0	2.1	
SD	0.85	0.63	0.63	0.74	
N	8	8	8	8	
Period: Week 2					
MEAN	2.3	2.7	2.4	1.9	
SD	0.57	0.71	0.70	0.42	
N	8	8	8	8	
Period: Week 4					
MEAN	2.3	2.4	2.3	1.6	
SD	0.68	0.75	0.51	0.56	
N	8	8	8	8	
Period: Week 8					
MEAN	2.4	2.9	2.0	1.8	
SD	0.54	0.63	0.53	0.61	
N	8	8	8	8	
Period: Week 13					
MEAN	2.5	2.5	1.9	2.3	
SD	0.81	0.88	0.24	1.25	
N	8	8	8	8	
Period: Week 18					
MEAN	2.6	2.5	2.1	2.0	
SD	1.28	0.54	0.26	1.28	
N	4	4	4	4	
Period: Week 26					
MEAN	2.3	2.1	2.4	2.4	
SD	0.74	0.43	0.52	0.82	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

Table 8.35

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Monocytes

STUDY ID: 097
STUDY NO: 097
ABBR: Monocytes

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.5	0.7	0.5	0.5	
SD	0.28	0.57	0.26	0.28	
N	8	8	8	8	
Period: Week -1					
MEAN	0.4	0.8	0.5	0.5	
SD	0.18	0.63	0.28	0.20	
N	8	8	8	8	
Period: Week 2					
MEAN	0.4	0.7	0.8	0.7	
SD	0.23	0.42	0.39	0.32	
N	8	8	8	8	
Period: Week 4					
MEAN	0.4	0.6	0.8	0.9*	
SD	0.14	0.17	0.35	0.51	
N	8	8	8	8	
Period: Week 8					
MEAN	0.4	0.6	0.8*	0.9*	
SD	0.18	0.32	0.21	0.31	
N	8	8	8	8	
Period: Week 13					
MEAN	0.5	0.6	0.9	1.0*	
SD	0.24	0.35	0.25	0.48	
N	8	8	8	8	
Period: Week 18					
MEAN	0.4	0.6	0.4	0.7	
SD	0.46	0.38	0.10	0.32	
N	4	4	4	4	
Period: Week 26					
MEAN	0.4	0.5	0.3	0.3	
SD	0.33	0.13	0.14	0.14	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Monocytes

STUDY ID: 097
STUDY NO: 097
ABBR: Monocytes

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.5	0.3	0.4	0.6	
SD	0.27	0.21	0.18	0.16	
N	8	8	8	8	
Period: Week -1					
MEAN	0.5	0.4	0.4	0.7	
SD	0.40	0.28	0.32	0.27	
N	8	8	8	8	
Period: Week 2					
MEAN	0.5	0.4	0.4	0.6	
SD	0.28	0.29	0.18	0.26	
N	8	8	8	8	
Period: Week 4					
MEAN	0.4	0.3	0.7*	0.8*	
SD	0.25	0.13	0.27	0.26	
N	8	8	8	8	
Period: Week 8					
MEAN	0.3	0.4	0.6	0.7*	
SD	0.12	0.29	0.25	0.27	
N	8	8	8	8	
Period: Week 13					
MEAN	0.4	0.3	0.7	1.1*	
SD	0.17	0.24	0.41	0.50	
N	8	8	8	8	
Period: Week 18					
MEAN	0.2	0.4	0.5	0.8	
SD	0.10	0.14	0.24	0.69	
N	4	4	4	4	
Period: Week 26					
MEAN	0.3	0.4	0.4	0.6	
SD	0.13	0.21	0.31	0.34	
N	4	4	4	4	

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Eosinophils

STUDY ID: 097
STUDY NO: 097
ABBR: Eosinophil

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.2	0.3	0.3	0.4	
SD	0.07	0.22	0.17	0.30	
N	8	8	8	8	
Period: Week -1					
MEAN	0.2	0.2	0.3	0.3	
SD	0.15	0.34	0.13	0.30	
N	8	8	8	8	
Period: Week 2					
MEAN	0.2	0.3	0.2	0.3	
SD	0.19	0.28	0.17	0.43	
N	8	8	8	8	
Period: Week 4					
MEAN	0.2	0.3	0.3	0.2	
SD	0.19	0.26	0.21	0.12	
N	8	8	8	8	
Period: Week 8					
MEAN	0.3	0.4	0.4	0.5	
SD	0.09	0.15	0.17	0.21	
N	8	8	8	8	
Period: Week 13					
MEAN	0.4	0.4	0.3	0.5	
SD	0.21	0.31	0.28	0.42	
N	8	8	8	8	
Period: Week 18					
MEAN	0.3	0.2	0.4	0.6	
SD	0.08	0.08	0.18	0.24	
N	4	4	4	4	
Period: Week 26					
MEAN	0.3	0.4	0.6	0.4	
SD	0.10	0.22	0.59	0.13	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Eosinophils

STUDY ID: 097
STUDY NO: 097
ABBR: Eosinophil

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.1	0.3	0.2	0.3	
SD	0.06	0.21	0.15	0.35	
N	8	8	8	8	
Period: Week -1					
MEAN	0.2	0.3	0.2	0.2	
SD	0.19	0.18	0.15	0.17	
N	8	8	8	8	
Period: Week 2					
MEAN	0.2	0.3	0.1	0.1	
SD	0.23	0.32	0.12	0.08	
N	8	8	8	8	
Period: Week 4					
MEAN	0.2	0.4*	0.1	0.2	
SD	0.20	0.22	0.15	0.11	
N	8	8	8	8	
Period: Week 8					
MEAN	0.1	0.3	0.2	0.3	
SD	0.17	0.14	0.19	0.12	
N	8	8	8	8	
Period: Week 13					
MEAN	0.2	0.3	0.2	0.3	
SD	0.22	0.26	0.14	0.25	
N	8	8	8	8	
Period: Week 18					
MEAN	0.2	0.3	0.2	0.3	
SD	0.10	0.13	0.10	0.13	
N	4	4	4	4	
Period: Week 26					
MEAN	0.3	0.6	0.1	0.6	
SD	0.34	0.65	0.13	0.38	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Basophils

STUDY ID: 097
STUDY NO: 097
ABBR: Basophils

SEX: MALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week -1					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 2					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 4					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 8					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 13					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 18					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	4	4	4	4	
Period: Week 26					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

SUMMARY OF HEMATOLOGICAL TESTS
TEST: Basophils

STUDY ID: 097
STUDY NO: 097
ABBR: Basophils

SEX: FEMALE

UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.1	2.0	6.0	mg base/kg/day
Period: Week -3					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week -1					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 2					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 4					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 8					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.04	0.00	0.00	
N	8	8	8	8	
Period: Week 13					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	8	8	8	8	
Period: Week 18					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	4	4	4	4	
Period: Week 26					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	4	4	4	4	

WBC corrected for NRBC = or > 10

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 097
SEX: MALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:		(1) 1M	(2) 2M	(3) 3M	(4) 4M
Adrenals (% BODY WEIGHT)					
	MEAN	0.010	0.014	0.013	0.017
	SD	0.0047	0.0036	0.0024	0.0046
	N	4	4	4	4
Brain (% BODY WEIGHT)					
	MEAN	0.746	0.706	0.723	0.827
	SD	0.0619	0.0675	0.0647	0.1600
	N	4	4	4	4
Heart (% BODY WEIGHT)					
	MEAN	0.898	0.853	0.876	0.953
	SD	0.0712	0.0804	0.0882	0.0849
	N	4	4	4	4
Kidneys (% BODY WEIGHT)					
	MEAN	0.485	0.504	0.507	0.558
	SD	0.0128	0.0205	0.0617	0.0638
	N	4	4	4	4
Liver (% BODY WEIGHT)					
	MEAN	2.449	2.607	3.066	3.866*
	SD	0.1686	0.2833	0.4269	0.5855
	N	4	4	4	4
Spleen (% BODY WEIGHT)					
	MEAN	0.303	0.299	0.409	0.580*
	SD	0.0491	0.0513	0.0908	0.1947
	N	4	4	4	4
Testes w/Epidid. (% BODY WEIGHT)					
	MEAN	0.130	0.169	0.165	0.196
	SD	0.0390	0.0231	0.0406	0.0277
	N	4	4	4	4
Thyroids-Parathyroids (% BODY WEIGHT)					
	MEAN	0.010	0.013	0.011	0.015
	SD	0.0015	0.0048	0.0023	0.0057
	N	3	4	4	4

(1)-0 mg base/kg/day
(2)-0.1 mg base/kg/day
(3)-2.0 mg base/kg/day
(4)-6.0 mg base/kg/day
* - Significant difference P<.05

Table 9.2

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 097
SEX: FEMALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
Adrenals (% BODY WEIGHT)					
	MEAN	0.014	0.014	0.015	0.016
	SD	0.0038	0.0025	0.0013	0.0059
	N	4	4	4	4
Brain (% BODY WEIGHT)					
	MEAN	0.735	0.898	0.900	0.880
	SD	0.0813	0.1052	0.1410	0.0949
	N	4	4	4	4
Heart (% BODY WEIGHT)					
	MEAN	0.852	0.959	0.969	0.889
	SD	0.0619	0.1261	0.1633	0.0198
	N	4	4	4	4
Kidneys (% BODY WEIGHT)					
	MEAN	0.439	0.461	0.490	0.502
	SD	0.0246	0.0373	0.0493	0.0371
	N	4	4	4	4
Liver (% BODY WEIGHT)					
	MEAN	2.674	2.753	3.443*	3.470*
	SD	0.0647	0.5699	0.3494	0.2169
	N	4	4	4	4
Ovaries (% BODY WEIGHT)					
	MEAN	0.011	0.013	0.009	0.011
	SD	0.0043	0.0045	0.0032	0.0020
	N	4	4	4	3
Spleen (% BODY WEIGHT)					
	MEAN	0.268	0.329	0.453	1.071*
	SD	0.0220	0.0707	0.1117	0.2153
	N	4	4	4	4
Thyroids-Parathyroids (% BODY WEIGHT)					
	MEAN	0.011	0.014	0.013	0.014
	SD	0.0024	0.0045	0.0010	0.0035
	N	4	4	4	4
Uterus (% BODY WEIGHT)					
	MEAN	0.076	0.061	0.070	0.075
	SD	0.0678	0.0342	0.0740	0.0413
	N	4	4	4	4

(5)-0 mg base/kg/day
(6)-0.1 mg base/kg/day
(7)-2.0 mg base/kg/day
(8)-6.0 mg base/kg/day
* - Significant difference P<.05

Table 9.3

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 097
SEX: MALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:		(1) 1M	(2) 2M	(3) 3M	(4) 4M
Adrenals (% BODY WEIGHT)					
	MEAN	0.010	0.013	0.015*	0.012
	SD	0.0022	0.0008	0.0021	0.0019
	N	4	4	4	4
Brain (% BODY WEIGHT)					
	MEAN	0.680	0.675	0.689	0.687
	SD	0.0642	0.0767	0.0682	0.0803
	N	4	4	4	4
Heart (% BODY WEIGHT)					
	MEAN	0.840	0.843	0.907	0.934
	SD	0.0402	0.1114	0.1188	0.1324
	N	4	4	4	4
Kidneys (% BODY WEIGHT)					
	MEAN	0.509	0.533	0.531	0.506
	SD	0.0597	0.0702	0.0546	0.0485
	N	4	4	4	4
Liver (% BODY WEIGHT)					
	MEAN	2.320	2.543	2.643	2.828
	SD	0.2361	0.2705	0.2094	0.3193
	N	4	4	4	4
Spleen (% BODY WEIGHT)					
	MEAN	0.310	0.315	0.359	0.307
	SD	0.0703	0.1097	0.0657	0.0476
	N	4	4	4	4
Testes w/Epidid. (% BODY WEIGHT)					
	MEAN	0.187	0.174	0.191	0.174
	SD	0.0223	0.0132	0.0283	0.0259
	N	4	4	4	4
Thyroids-Parathyroids (% BODY WEIGHT)					
	MEAN	0.009	0.009	0.014*	0.013*
	SD	0.0021	0.0012	0.0026	0.0017
	N	4	4	4	4

(1)-0 mg base/kg/day
(2)-0.1 mg base/kg/day
(3)-2.0 mg base/kg/day
(4)-6.0 mg base/kg/day
* - Significant difference P<.05

Table 9.4

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 097
SEX: FEMALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
Adrenals (% BODY WEIGHT)					
	MEAN	0.015	0.013	0.015	0.013
	SD	0.0035	0.0025	0.0025	0.0021
	N	4	4	4	4
Brain (% BODY WEIGHT)					
	MEAN	0.745	0.711	0.765	0.783
	SD	0.1410	0.0719	0.0517	0.1018
	N	4	4	4	4
Heart (% BODY WEIGHT)					
	MEAN	0.799	0.775	0.859	0.832
	SD	0.1203	0.1390	0.1384	0.0722
	N	4	4	4	4
Kidneys (% BODY WEIGHT)					
	MEAN	0.409	0.399	0.431	0.469
	SD	0.0423	0.0505	0.0536	0.0191
	N	4	4	4	4
Liver (% BODY WEIGHT)					
	MEAN	2.425	2.464	2.789	3.051
	SD	0.2782	0.4558	0.6472	0.1663
	N	4	4	4	4
Ovaries (% BODY WEIGHT)					
	MEAN	0.014	0.014	0.013	0.019
	SD	0.0054	0.0046	0.0031	0.0082
	N	4	4	4	4
Spleen (% BODY WEIGHT)					
	MEAN	0.323	0.298	0.338	0.349
	SD	0.0199	0.0719	0.0978	0.0505
	N	4	4	4	4
Thyroids-Parathyroids (% BODY WEIGHT)					
	MEAN	0.011	0.009	0.011	0.010
	SD	0.0014	0.0021	0.0022	0.0017
	N	4	4	4	4
Uterus (% BODY WEIGHT)					
	MEAN	0.092	1.157	0.090	0.149
	SD	0.0908	2.1270	0.0495	0.0737
	N	4	4	4	4

(5)-0 mg base/kg/day
(6)-0.1 mg base/kg/day
(7)-2.0 mg base/kg/day
(8)-6.0 mg base/kg/day

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 097
SEX: MALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(1) 1M	(2) 2M	(3) 3M	(4) 4M
Adrenals (% BRAIN WEIGHT)				
MEAN	1.36	1.94	1.75	2.08
SD	0.695	0.397	0.287	0.663
N	4	4	4	4
Heart (% BRAIN WEIGHT)				
MEAN	121.60	121.06	121.26	116.97
SD	19.188	8.041	6.641	12.555
N	4	4	4	4
Kidneys (% BRAIN WEIGHT)				
MEAN	65.33	71.78	70.07	68.27
SD	5.116	6.172	6.134	5.032
N	4	4	4	4
Liver (% BRAIN WEIGHT)				
MEAN	330.49	369.79	424.46*	470.60*
SD	38.673	31.076	47.561	24.148
N	4	4	4	4
Spleen (% BRAIN WEIGHT)				
MEAN	40.91	42.34	56.35	69.97*
SD	8.242	6.401	9.894	15.844
N	4	4	4	4
Testes w/Epidid. (% BRAIN WEIGHT)				
MEAN	17.37	23.95	22.98	24.58
SD	5.031	2.563	5.867	7.119
N	4	4	4	4
Thyroids-Parathyroids (% BRAIN WEIGHT)				
MEAN	1.34	1.76	1.55	1.94
SD	0.146	0.570	0.224	0.972
N	3	4	4	4

(1)-0 mg base/kg/day
(2)-0.1 mg base/kg/day
(3)-2.0 mg base/kg/day
(4)-6.0 mg base/kg/day

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 097
SEX: FEMALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
Adrenals (% BRAIN WEIGHT)					
	MEAN	1.84	1.60	1.63	1.77
	SD	0.340	0.188	0.256	0.786
	N	4	4	4	4
Heart (% BRAIN WEIGHT)					
	MEAN	116.84	106.95	107.96	101.85
	SD	11.824	7.097	11.091	11.268
	N	4	4	4	4
Kidneys (% BRAIN WEIGHT)					
	MEAN	60.11	51.77	55.07	57.38
	SD	5.098	6.701	5.272	5.046
	N	4	4	4	4
Liver (% BRAIN WEIGHT)					
	MEAN	367.60	308.81	387.66	399.52
	SD	43.059	68.227	50.366	66.293
	N	4	4	4	4
Ovaries (% BRAIN WEIGHT)					
	MEAN	1.52	1.51	1.07	1.26
	SD	0.751	0.678	0.587	0.093
	N	4	4	4	3
Spleen (% BRAIN WEIGHT)					
	MEAN	36.71	36.43	51.15	122.80*
	SD	4.091	3.997	12.883	28.050
	N	4	4	4	4
Thyroids-Parathyroids (% BRAIN WEIGHT)					
	MEAN	1.53	1.57	1.52	1.54
	SD	0.212	0.579	0.333	0.263
	N	4	4	4	4
Uterus (% BRAIN WEIGHT)					
	MEAN	11.01	7.14	9.01	8.43
	SD	10.812	4.806	11.283	4.464
	N	4	4	4	4

(5)-0 mg base/kg/day
(6)-0.1 mg base/kg/day
(7)-2.0 mg base/kg/day
(8)-6.0 mg base/kg/day
*-Significant Difference from Control P < .05

Table 10.3

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 097
SEX: MALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(1) 1M	(2) 2M	(3) 3M	(4) 4M
Adrenals (% BRAIN WEIGHT)				
MEAN	1.51	1.96	2.22*	1.72
SD	0.254	0.375	0.317	0.217
N	4	4	4	4
Heart (% BRAIN WEIGHT)				
MEAN	124.23	125.45	131.51	136.12
SD	11.359	14.775	6.651	14.041
N	4	4	4	4
Kidneys (% BRAIN WEIGHT)				
MEAN	75.53	79.94	77.19	74.55
SD	13.542	14.503	5.104	12.126
N	4	4	4	4
Liver (% BRAIN WEIGHT)				
MEAN	344.79	379.00	387.04	412.22
SD	60.512	46.066	54.677	18.890
N	4	4	4	4
Spleen (% BRAIN WEIGHT)				
MEAN	45.56	46.27	52.82	44.85
SD	8.922	13.200	12.708	6.772
N	4	4	4	4
Testes w/Epidid. (% BRAIN WEIGHT)				
MEAN	27.67	25.95	27.57	25.23
SD	4.062	2.967	1.876	1.535
N	4	4	4	4
Thyroids-Parathyroids (% BRAIN WEIGHT)				
MEAN	1.37	1.39	1.93*	1.93*
SD	0.184	0.205	0.302	0.281
N	4	4	4	4

(1)-0 mg base/kg/day
(2)-0.1 mg base/kg/day
(3)-2.0 mg base/kg/day
(4)-6.0 mg base/kg/day
* - Significant difference P<.05

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 097
SEX: FEMALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
Adrenals (% BRAIN WEIGHT)				
MEAN	1.96	1.85	1.94	1.64
SD	0.270	0.201	0.205	0.199
N	4	4	4	4
Heart (% BRAIN WEIGHT)				
MEAN	107.87	108.40	111.90	108.10
SD	7.052	11.033	11.489	21.085
N	4	4	4	4
Kidneys (% BRAIN WEIGHT)				
MEAN	55.55	56.05	56.22	60.58
SD	6.025	4.596	3.517	6.868
N	4	4	4	4
Liver (% BRAIN WEIGHT)				
MEAN	328.95	348.56	362.84	395.86
SD	30.562	69.861	64.689	65.485
N	4	4	4	4
Ovaries (% BRAIN WEIGHT)				
MEAN	1.79	1.97	1.64	2.48
SD	0.486	0.740	0.489	1.224
N	4	4	4	4
Spleen (% BRAIN WEIGHT)				
MEAN	44.75	41.49	44.96	44.89
SD	9.441	6.886	15.084	7.268
N	4	4	4	4
Thyroids-Parathyroids (% BRAIN WEIGHT)				
MEAN	1.49	1.22	1.42	1.27
SD	0.255	0.208	0.248	0.381
N	4	4	4	4
Uterus (% BRAIN WEIGHT)				
MEAN	11.18	179.65	11.94	19.65
SD	8.576	333.633	6.957	9.662
N	4	4	4	4

(5)-0 mg base/kg/day
(6)-0.1 mg base/kg/day
(7)-2.0 mg base/kg/day
(8)-6.0 mg base/kg/day

Table 11.1

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (ABSOLUTE)

STUDY: 097
SEX: MALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(1) 1M	(2) 2M	(3) 3M	(4) 4M
BODY WEIGHT (KG)					
	MEAN	11.0	10.8	10.4	9.6
	SD	0.57	0.57	0.56	1.12
	N	4	4	4	4
Adrenals (pr) (G)					
	MEAN	1.08	1.48	1.31	1.60
	SD	0.485	0.363	0.189	0.450
	N	4	4	4	4
Brain (G)					
	MEAN	82.02	76.09	75.22	77.66
	SD	8.041	6.445	5.829	6.315
	N	4	4	4	4
Heart (G)					
	MEAN	98.66	91.90	91.03	90.35
	SD	7.157	6.469	5.687	5.857
	N	4	4	4	4
Kidneys (pr) (G)					
	MEAN	53.32	54.42	52.79	52.79
	SD	2.670	3.708	7.254	1.059
	N	4	4	4	4
Liver (G)					
	MEAN	269.66	280.72	318.09*	364.36*
	SD	26.857	23.914	30.776	11.850
	N	4	4	4	4
Spleen (G)					
	MEAN	33.09	32.17	42.74	54.61*
	SD	4.127	4.965	10.574	14.612
	N	4	4	4	4
Testes w/Epidid. (pr) (G)					
	MEAN	14.28	18.20	17.14	18.86
	SD	4.173	2.115	3.822	4.694
	N	4	4	4	4
Thyroids-Parathyroids (G)					
	MEAN	1.08	1.34	1.17	1.46
	SD	0.163	0.419	0.221	0.658
	N	3	4	4	4

(1)-0 mg base/kg/day
(2)-0.1 mg base/kg/day
(3)-2.0 mg base/kg/day
(4)-6.0 mg base/kg/day
* - Significant difference P<.05

Table 11.2

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (ABSOLUTE)

STUDY: 097
SEX: FEMALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
BODY WEIGHT (KG)					
	MEAN	9.3	8.6	8.6	8.3
	SD	1.15	1.27	1.42	0.98
	N	4	4	4	4
Adrenals (pr) (G)					
	MEAN	1.25	1.21	1.24	1.28
	SD	0.241	0.080	0.192	0.586
	N	4	4	4	4
Brain (G)					
	MEAN	67.43	76.09*	75.88*	72.01
	SD	1.652	5.262	2.420	3.663
	N	4	4	4	4
Heart (G)					
	MEAN	78.77	81.34	81.78	73.28
	SD	8.087	7.248	6.843	8.384
	N	4	4	4	4
Kidneys (pr) (G)					
	MEAN	40.53	39.39	41.77	41.22
	SD	3.673	6.025	3.989	2.587
	N	4	4	4	4
Liver (G)					
	MEAN	248.16	235.15	293.69	287.16
	SD	32.975	56.655	34.027	46.994
	N	4	4	4	4
Ovaries (G)					
	MEAN	1.03	1.15	0.81	0.90
	SD	0.535	0.551	0.428	0.104
	N	4	4	4	3
Spleen (G)					
	MEAN	24.80	27.61	38.89	87.78*
	SD	3.323	2.145	10.249	16.033
	N	4	4	4	4
Thyroids-Parathyroids (G)					
	MEAN	1.03	1.19	1.15	1.12
	SD	0.141	0.448	0.238	0.237
	N	4	4	4	4
Uterus (G)					
	MEAN	7.51	5.48	6.76	6.12
	SD	7.566	3.920	8.355	3.288
	N	4	4	4	4

(5)-0 mg base/kg/day
(6)-0.1 mg base/kg/day
(7)-2.0 mg base/kg/day
(8)-6.0 mg base/kg/day
* - Significant difference P<.05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (ABSOLUTE)

STUDY: 097
SEX: MALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(1) 1M	(2) 2M	(3) 3M	(4) 4M
BODY WEIGHT (KG)					
	MEAN	11.6	11.3	11.3	10.8
	SD	0.84	0.79	1.10	0.80
	N	4	4	4	4
Adrenals (pr) (G)					
	MEAN	1.17	1.47	1.72*	1.27
	SD	0.151	0.203	0.299	0.168
	N	4	4	4	4
Brain (G)					
	MEAN	78.51	75.57	77.54	74.09
	SD	8.550	5.577	4.043	9.390
	N	4	4	4	4
Heart (G)					
	MEAN	96.88	94.28	101.98	100.46
	SD	4.431	6.841	7.506	12.046
	N	4	4	4	4
Kidneys (pr) (G)					
	MEAN	58.49	59.84	59.70	54.46
	SD	5.274	7.446	1.220	3.804
	N	4	4	4	4
Liver (G)					
	MEAN	267.73	285.02	300.01	305.73
	SD	30.590	23.798	45.750	44.152
	N	4	4	4	4
Spleen (G)					
	MEAN	36.19	35.28	40.81	33.12
	SD	10.821	11.931	9.441	5.486
	N	4	4	4	4
Testes w/Epidid. (pr) (G)					
	MEAN	21.66	19.50	21.35	18.69
	SD	3.315	1.130	1.300	2.544
	N	4	4	4	4
Thyroids-Parathyroids (G)					
	MEAN	1.08	1.04	1.49*	1.41*
	SD	0.202	0.093	0.188	0.105
	N	4	4	4	4

(1)-0 mg base/kg/day
(2)-0.1 mg base/kg/day
(3)-2.0 mg base/kg/day
(4)-6.0 mg base/kg/day
* - Significant difference P<.05

Table 11.4

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

ORGAN WEIGHT SUMMARY (ABSOLUTE)

STUDY: 097
SEX: FEMALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
BODY WEIGHT (KG)					
	MEAN	10.1	10.6	9.6	9.7
	SD	1.33	0.85	0.92	1.12
	N	4	4	4	4
Adrenals (pr) (G)					
	MEAN	1.45	1.38	1.41	1.23
	SD	0.179	0.164	0.180	0.057
	N	4	4	4	4
Brain (G)					
	MEAN	74.15	75.04	72.72	75.26
	SD	4.819	4.711	4.287	5.986
	N	4	4	4	4
Heart (G)					
	MEAN	79.76	81.48	81.04	80.78
	SD	2.387	11.300	4.611	12.757
	N	4	4	4	4
Kidneys (pr) (G)					
	MEAN	40.98	42.04	40.80	45.48
	SD	2.146	4.152	1.706	5.202
	N	4	4	4	4
Liver (G)					
	MEAN	242.81	262.27	261.93	297.10
	SD	7.464	60.012	34.082	49.394
	N	4	4	4	4
Ovaries (G)					
	MEAN	1.35	1.48	1.19	1.83
	SD	0.431	0.576	0.313	0.813
	N	4	4	4	4
Spleen (G)					
	MEAN	32.95	31.18	32.64	33.83
	SD	6.063	5.888	10.547	6.794
	N	4	4	4	4
Thyroids-Parathyroids (G)					
	MEAN	1.10	0.92	1.02	0.94
	SD	0.133	0.207	0.128	0.217
	N	4	4	4	4
Uterus (G)					
	MEAN	8.54	133.48	8.56	14.76
	SD	7.095	247.225	4.705	7.337
	N	4	4	4	4

(5)-0 mg base/kg/day
(6)-0.1 mg base/kg/day
(7)-2.0 mg base/kg/day
(8)-6.0 mg base/kg/day

Table 12

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN DOGS

Summary of Microscopic Lesions[a]

ORGAN - lesion	Sex	Dose (mg base/kg/day) 0	0.1	2.0	6.0	0 - R	0.2 - R	2.0 - R	6.0 - R
LUNGS									
- Alveolar proteinosis	M	0/4 (0.00)	0/4 (0.00)	2/4 (0.50)	4/4 (2.50)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
	F	0/4 (0.00)	0/4 (0.00)	4/4 (1.00)	4/4 (2.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	2/4 (0.50)
- Subacute inflammation	M	1/4 (0.25)	2/4 (0.50)	4/4 (2.50)	4/4 (3.25)	2/4 (0.50)	2/4 (0.50)	3/4 (0.75)	4/4 (1.25)
	F	2/4 (1.00)	4/4 (1.25)	4/4 (2.75)	4/4 (2.25)	3/4 (0.75)	1/4 (0.50)	4/4 (1.00)	4/4 (1.50)
- Chronic inflammation	M	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	2/4 (0.75)	3/4 (1.00)
	F	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	1/4 (0.50)	1/4 (0.25)	2/4 (0.50)	0/4 (0.00)
SPLEEN									
- Extramedullary hematopoiesis	M	0/4 (0.00)	0/4 (0.00)	1/4 (0.25)	2/4 (0.50)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
	F	0/4 (0.00)	0/4 (0.00)	1/4 (0.25)	3/4 (1.25)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
- Hemosiderin pigment	M	0/4 (0.00)	1/4 (0.25)	1/4 (0.50)	3/4 (1.00)	2/4 (0.75)	1/4 (0.25)	1/4 (0.25)	2/4 (0.50)
	F	0/4 (0.00)	0/4 (0.00)	3/4 (1.00)	4/4 (1.25)	1/4 (0.25)	0/4 (0.00)	3/4 (0.75)	3/4 (1.00)
LIVER									
- Hemosiderin pigment	M	0/4 (0.00)	0/4 (0.00)	2/4 (0.75)	1/4 (0.75)	0/4 (0.00)	0/4 (0.00)	1/4 (0.25)	2/4 (0.75)
	F	0/4 (0.00)	1/4 (0.25)	2/4 (1.00)	4/4 (2.25)	0/4 (0.00)	0/4 (0.00)	4/4 (1.00)	3/4 (1.25)
- Kupffer cell hypertrophy	M	0/4 (0.00)	0/4 (0.00)	1/4 (0.25)	2/4 (0.75)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
	F	0/4 (0.00)	0/4 (0.00)	1/4 (0.50)	4/4 (2.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
- Subacute inflammation	M	0/4 (0.00)	1/4 (0.25)	1/4 (0.25)	1/4 (0.75)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
	F	0/4 (0.00)	0/4 (0.00)	1/4 (0.50)	4/4 (1.75)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
- Hepatocyte necrosis	M	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	2/4 (0.50)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
	F	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
THYMUS									
- Lymphocyte depletion	M	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	3/4 (1.75)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
	F	0/4 (0.00)	0/4 (0.00)	1/4 (0.50)	1/4 (0.25)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
BONE MARROW									
- Hypercellularity	M	0/4 (0.00)	1/4 (0.25)	1/4 (0.25)	4/4 (1.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
	F	0/4 (0.00)	0/4 (0.00)	4/4 (1.00)	4/4 (1.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)	0/4 (0.00)
- M/E Ratio	M	-	NE	↓	↓	-	NE	NE	NE
	F	-	NE	↓	↓	-	NE	NE	NE

[a]Incidence (mean group severity) - Determined by dividing the sum of all severity scores for a finding by the number of tissues examined. See Pathology Report in Appendix 11.

R = Recovery groups NE = No effect

FIGURE 1
SUMMARY OF MALE BODY WEIGHTS

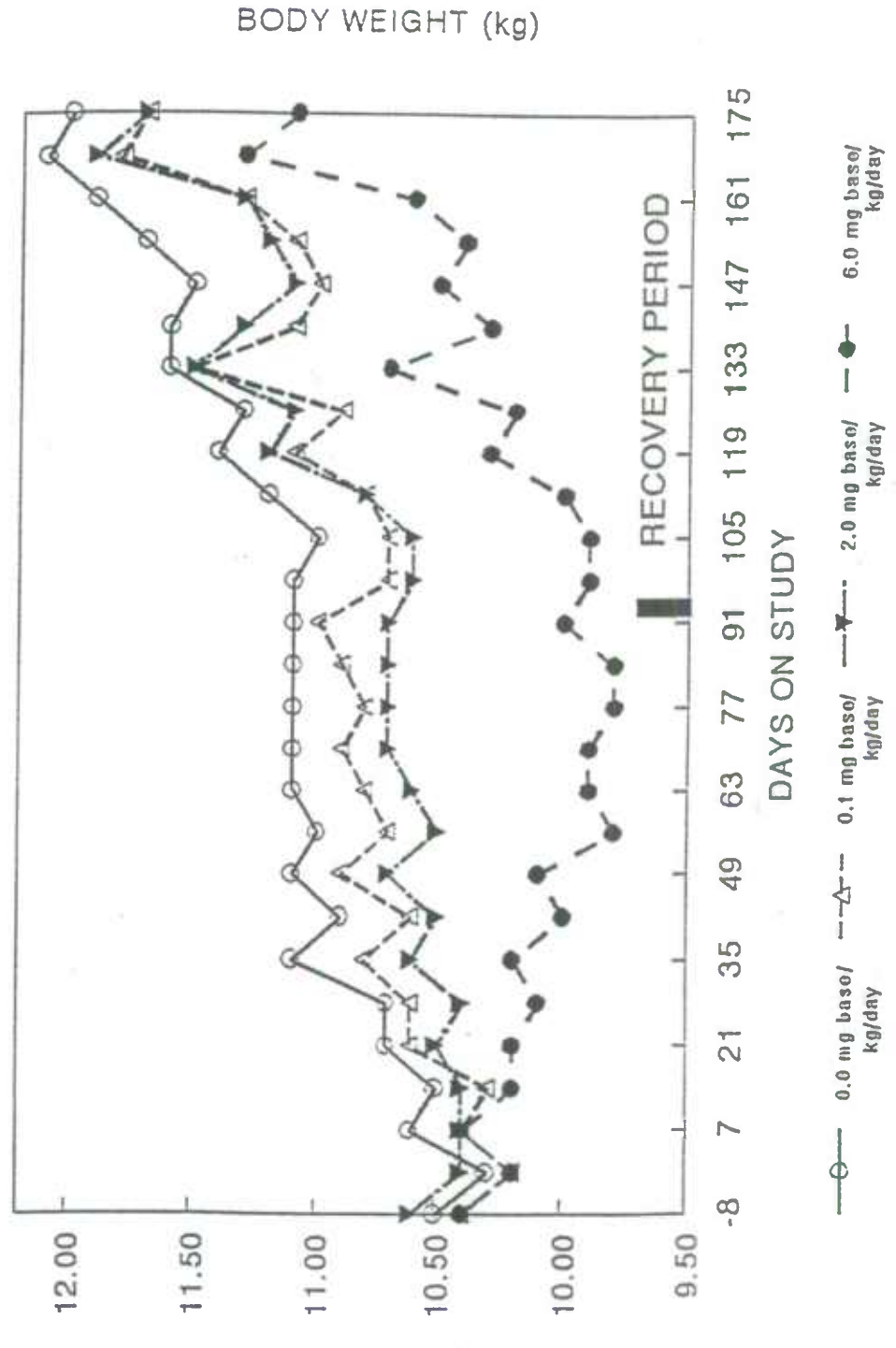

FIGURE 2

SUMMARY OF FEMALE BODY WEIGHTS